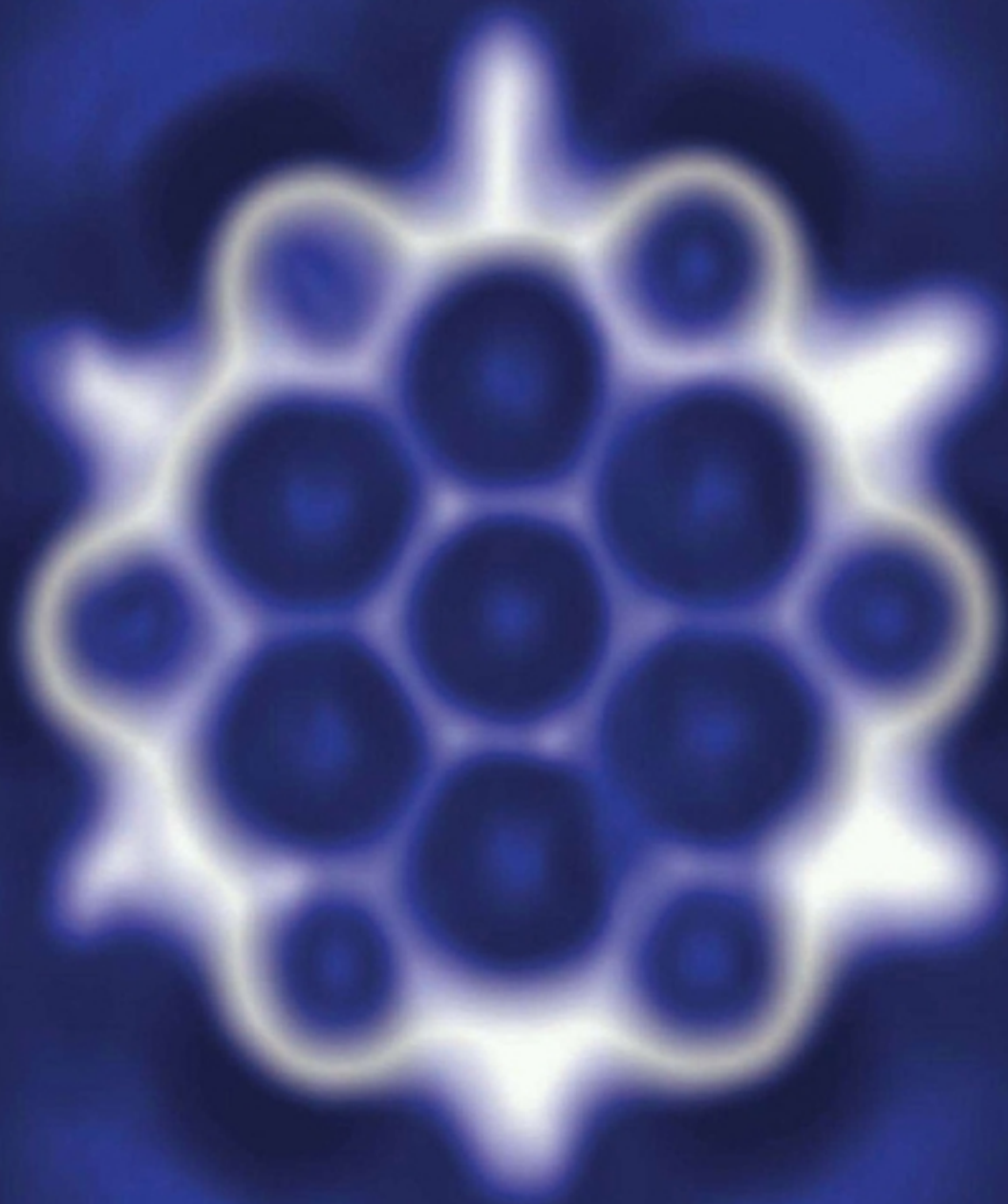


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# Science



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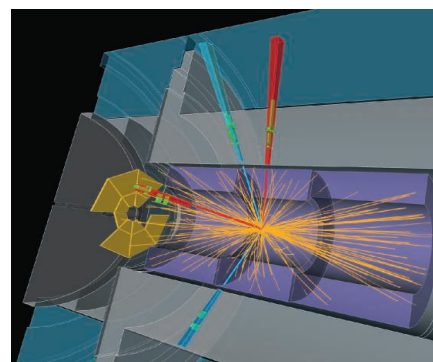
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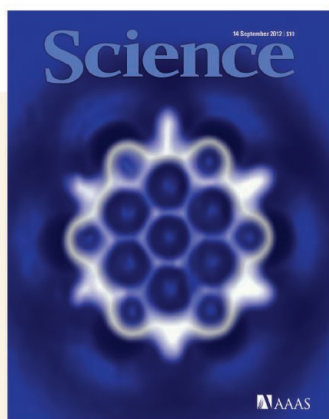
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A hexabenzocoronene molecule (diameter: 1.4 nanometers) imaged by noncontact atomic force microscopy using a microscope tip terminated with a single carbon monoxide molecule. The carbon-carbon bonds in the imaged molecule appear with different contrast and apparent lengths. Based on these disparities, the bond orders and lengths of the individual bonds can be distinguished. See page 1326.

*Image: Leo Gross, IBM Research - Zurich*

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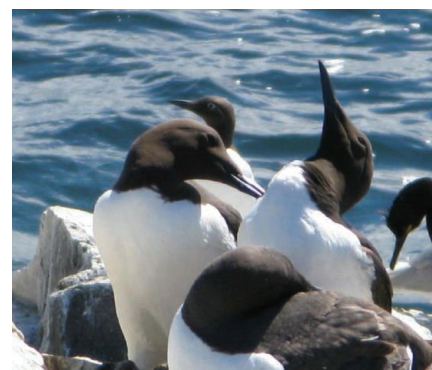
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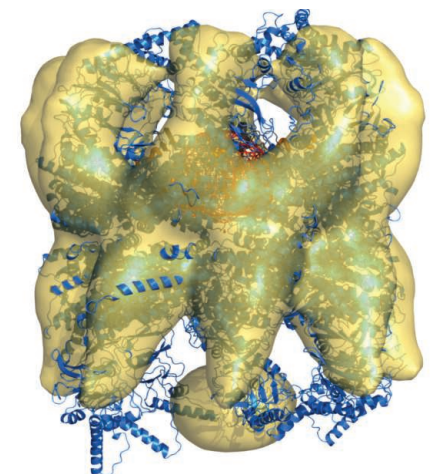
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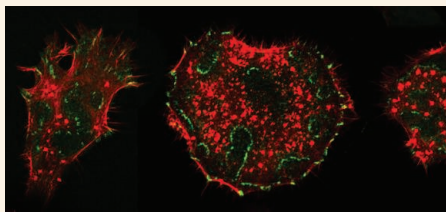


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Focal adhesions and invadopodia.

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10.1126/science.1226121

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Full text at [www.sciencemag.org/cgi/content/full/337/6100/1294-c](http://www.sciencemag.org/cgi/content/full/337/6100/1294-c)

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## Highlights From Our Daily News Coverage

## Slippery When Windy

Spray from whitecaps inside strong hurricanes renders a wavy ocean aerodynamically smooth.

<http://scim.ag/Slippery-Windy>

## Human Genome Is Much More Than Just Genes

The genome has billions of elements that switch genes on and off.

<http://scim.ag/Genome-Elements>

## Hunting Kills Boldest Elk, Spares Shiest

The behavior of elk could shift over time because of hunters' preferences.

<http://scim.ag/Elk-Behavior>

## SCIENCE SIGNALING

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## The Signal Transduction Knowledge Environment

11 September issue: <http://scim.ag/ss091112>RESEARCH ARTICLE: Network Analysis of the Focal Adhesion to Invadopodia Transition Identifies a PI3K-PKC $\alpha$  Invasive Signaling Axis

D. Hoshino et al.

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The activity of the lipid kinase PI3K governs whether the protein kinase PKC $\alpha$  promotes invasive behavior of cancer cells.

## RESEARCH ARTICLE: The Membrane-Bound Enzyme CD38 Exists in Two Opposing Orientations

Y. J. Zhao et al.

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## PERSPECTIVE: Revisiting the Nucleolus—From Marker to Dynamic Integrator of Cancer Signaling

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## SCIENCE CAREERS

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## Communications Tech Transforms Laboratories

J. Austin

The Internet and ubiquitous video are changing how science is done.

<http://scim.ag/CommTechLab>

## Must a Paper Trail Be Paper?

S. Carpenter

Most scientists continue to use tried-and-true paper lab notebooks, but electronic alternatives beckon some.

<http://scim.ag/PaperBePaper>

## YouTube at the Bench

V. Venkatraman

Video technology has the potential to dramatically improve the dissemination of lab protocols and techniques.

<http://scim.ag/VideoBench>

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Unregulated and medically unsupported stem cell-based treatments are being advertised online directly to consumers, requiring policy reform to protect patient safety.

## SCIENCE PODCAST

www.sciencemag.org/multimedia/podcast

Free Weekly Show

On the 14 September Science Podcast: grandma killer whales, who invented the Higgs, do-it-yourself lab equipment, and more.

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## Cooling Year-Round

Ice cores from Greenland show that several abrupt cooling events occurred during the last glacial period and early Holocene—two of the most dramatic being the Younger Dryas [which lasted from around 12.9 to 11.7 thousand years ago (ka)] and 8.2-ka event (which began around 8200 years ago and lasted for ~150 years). Wintertime temperatures in Greenland during the Younger Dryas seem to have been relatively lower than summertime temperatures although it is not clear if the 8.2-ka event experienced the same pattern of seasonal cooling. **Young et al.** (p. 1330) report observations of the positions of the leading edge of the Laurentide Ice Sheet and mountain glaciers on Baffin Island during the 8.2-ka event and find that mountain glaciers were larger than their predecessors during the Younger Dryas. It seems that cooling during the 8.2-ka event was more evenly distributed across the seasons than it was during that earlier cold period.

## An Eight-Noded Monster

In superconductors, electrons are bound into pairs, and the exact form of that pairing and the resulting energy gap can vary, depending on the details of the electron-electron interaction and the band structure of the material. The energy gaps of the recently discovered iron-based superconductors exhibit a variety of pairing functions.  $\text{KFe}_2\text{As}_2$  has been suggested to have a *d*-wave gap, similar to cuprate superconductors. **Okazaki et al.** (p. 1314) use laser-based angle-resolved photoemission spectroscopy (ARPES) to map out the superconducting gap on three Fermi surfaces (FS) of the compound. They find a different gap structure on each, with the middle FS gap vanishing at eight distinct positions (nodes). It appears that the gap respects the tetragonal symmetry of the crystal, indicating (although the details may vary) that all iron-based superconductors have an extended *s*-wave—symmetric pairing—a finding that will help understanding of unconventional superconductivity.

## Killer Eradication

Rinderpest is the second disease to be eradicated globally after smallpox. **Mariner et al.** (p. 1309) review the technical and social challenges that

were overcome during the course of eradication. Key achievements were the development of a thermostable vaccine, the recruitment of the pastoralists themselves for training and administration of vaccine, and complete vaccination coverage, despite occasionally hazardous environmental and political conditions. Although these achievements offer important lessons for future human and animal health programs, institutional memories are surprisingly short-lived, and it is important to document these lessons for the next eradication campaign.

## Visualizing Bond Order

Bond lengths in conjugated molecules closely reflect individual bond order and are usually determined by diffraction methods. It is valuable to know bond order for rationalizing aromaticity, and reactivity and for chemical structure determination. **Gross et al.** (p. 1326; see the Perspective by **Perez** and the cover) differentiated the bond orders in individual molecules in the fullerene  $\text{C}_{60}$  and in polyaromatic hydrocarbons by imaging with noncontact atomic force microscopy (AFM). The molecules were adsorbed onto a copper surface, and the AFM tip was decorated with a

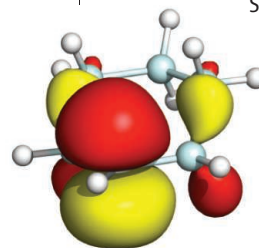
CO molecule, which was used to measure tip frequency shifts above the bonds and their apparent lengths. Multiple bonds appeared brighter in the images because of stronger Pauli repulsion, and their shorter length was amplified by bending of the CO at the tip apex.

## Conquering Rice Sterility

The hybrid sterility occurring among rice species has long been a puzzle and hampers progress in breeding crops with improved performance and yield characteristics. **Yang et al.** (p. 1336) have identified three linked genes encoding a killer, a partner, and a protector protein. The killer and partner work together to kill female gametes not carrying the functional protector, resulting in preferential transmission of gametes carrying the functional protector, which also causes segregation distortion in the progeny. This explanation for how reproductive isolation is maintained among species of rice, and perhaps other organisms, also offers approaches for boosting yields by intersubspecific heterosis.

## Fluorine's Smooth Introduction

Carbon-fluorine bonds are emerging as increasingly versatile constituents of drugs, agrochemicals, and positron emission tomography tracers. Elemental  $\text{F}_2$  gas is in principle an efficient reagent for their preparation, but its extreme reactivity requires special handling precautions.



Substantial research has therefore focused on promoting selective reactivity of more conveniently handled fluoride ion salts. **Liu et al.** (p. 1322) present a manganese catalyst that transfers fluoride to a range of hydrocarbons in conjunction with a hypervalent iodine-based oxidant. Mechanistic studies implicate a manganese difluoride intermediate that reacts with alkyl radicals generated by a preceding manganese oxo.

## Infectious Phenotype

The pathogenic yeast *Candida albicans* needs to adopt a filamentous form to invade tissues. The distantly related yeast species *Saccharomyces cerevisiae* also takes on a filamentous form for

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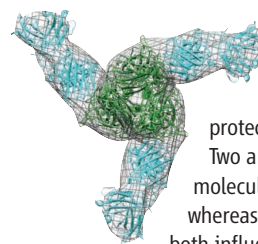
nutrient foraging. Comparing genome-wide deletion libraries between the two species, **Ryan *et al.*** (p. 1353) identified genes involved in three different filamentous yeast phenotypes and found unique genes for each of these phenotypes. However, in addition, core genes, including a previously unknown conserved regulator, appear to have homologous roles in regulating filamentous growth in these distantly related yeast species.

## Dissecting SNARE Zippering

The SNARE complex is critical for vesicle fusion, notably during release of neurotransmitters at synapses. Understanding the biophysics of SNARE assembly has been the object of several structural studies, and yet much remains to be understood about the mechanisms. Now, **Gao *et al.*** (p. 1340, published online 16 August; see the Perspective by **Rizo**) describe the results of cell-free experiments using optical tweezers to elucidate assembly and disassembly of the SNARE complex. Direct observations of SNARE intermediates revealed multiple steps of the assembly process, along with the associated energetics and kinetics. Applying forces similar to those occurring during fusion, an intermediate was stabilized, and the derived mechanism indicates how neurotransmitter release may be regulated.

## Influenza Antibodies, Part B

With its ability to reassort in animal hosts like pigs and birds, and to cause pandemics, influenza A viruses are often in the spotlight. However, a substantial portion of the annual flu burden is also the result of influenza B virus,

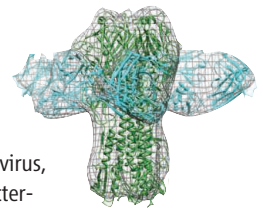


which is a single influenza type that is characterized by two antigenically and genetically distinct lineages. **Dreyfus *et al.*** (p. 1343, published online 9 August)

identify three monoclonal human antibodies that are able to protect against lethal infection with both lineages of influenza B virus in mice.

Two antibodies, which bind to distinct regions of the viral hemagglutinin (HA) molecule, neutralize multiple strains from both lineages of influenza B virus, whereas the third antibody binds to the stem region of HA and is able to neutralize both influenza A and B strains. The structural data from these antibodies bound to HA, together with already known antibodies targeting influenza A, may provide clues

for designing a universal vaccine to protect against both influenza virus types.



## A Critical Period for Glia

The brain develops in fits and starts—while one system is completed, another system may still be under construction. Such transient states are known as critical periods, and during these specific aspects of brain development may become more sensitive to outside agents than they would be later. **Makinodan *et al.*** (p. 1357) observed the effect of environmental conditions on the brains of mice bioengineered to develop fluorescent oligodendrocytes. The mice were exposed to a variety of social conditions during rearing, ranging from isolation to a normal laboratory cage setting, or to settings enriched with extra buddies and a steady rotation of new play toys. The results show that social isolation leaves a developmental trace that persists into adulthood. Specifically, they found that oligodendrocytes, which produce the myelin that insulates neurons, were underdeveloped, suggesting that there may be a critical period that governs development of these glial oligodendrocyte cells.

## Intergenerational Transposable Shutdown

Transposable elements (TEs) are a potential threat, especially to the germline genome. In many eukaryotes, TEs are shut down by DNA methylation and/or small-RNA-mediated silencing. Therefore, it seems counterintuitive that results obtained by **Ibarra *et al.*** (p. 1360) on *Arabidopsis* showed that in the cells of this plant's sexual apparatus, many small TEs are demethylated by DEMETER (DME) DNA glycosylase and become activated. But it turns out that activation of the TEs triggers the formation of small-interfering RNAs, which in these experiments were seen to travel from the surrounding cells to the egg. Thus, activation of TEs in the companion cells “immunizes” the gametes via the interfering RNAs that shutdown the TEs in the gametes permanently.



Paul Berg is the Cahill Professor of Biochemistry, Emeritus, at the Stanford University School of Medicine, Palo Alto, CA. He received the Nobel Prize in Chemistry in 1980 and was an organizer of the Asilomar conference on recombinant DNA in 1975. E-mail: pberg@stanford.edu.

## The Dual-Use Conundrum

SCIENTISTS ARE INCREASINGLY ABLE TO CREATE GENETICALLY MODIFIED MICROORGANISMS WHOSE properties are perceived as being beneficial as well as potentially useful for malevolent purposes. In 2004, a committee of the U.S. National Academy of Sciences adopted the term “dual use” for instances in which genetic or biosynthetic manipulations create new microorganisms, which, although valuable scientifically, are susceptible to misuse.\* The premise was that the prospects for malevolent outcomes derive from deliberate actions to inflict specific or widespread harm. But in those and subsequent discussions, too little attention was given to the likelihood of an accidental laboratory release of modified agents that would allow them to spread in susceptible human populations. Recent research with a highly pathogenic influenza virus has highlighted the importance of this issue. Reviews of the influenza research concluded that given “the risk of accidental or malicious release,” the benefits of such studies must be well justified.† Thus, specific guidelines must be enforced to thwart not only intentionally harmful outcomes but accidental releases as well.

The 2004 committee recommended that individual scientists and the editors of scientific journals exercise responsible judgment in undertaking and publishing experiments that describe the creation of, or could lead to, such biological agents of concern. This led to the creation of the U.S. National Science Advisory Board for Biosecurity (NSABB) to advise the federal government on policies governing publication, public communication, and dissemination of dual-use research methodologies and results. Recognizing that identifying all experiments or products of potential misuse was problematic, the NSABB adopted the term “dual-use research of concern” to focus on those entities that could, if misused, cause grave harm on a large scale.

Earlier this year, the NSABB was embroiled in a high-profile decision regarding the publication of research on enhanced transmissibility of the avian H5N1 influenza virus. The principal concern was that publishing such findings might embolden those with sinister motives to use that information to create a worldwide pandemic. The final outcome was to publish the papers in their entirety, reflecting a judgment that the risk of malicious actions was less than the benefits investigators would derive from an enhanced capability to design protective measures.‡ Throughout that debate, far less attention was given to the probabilities of inadvertent release of the modified viral strains and the consequences for susceptible human populations. Past experience provides a useful lesson. In the 1970s, accidental release was at the center of the biosafety debate generated by the advent of recombinant DNA technology. A meeting of scientists at Asilomar in 1975 resulted in federal and institutional oversight and regulation of recombinant DNA research. In that case, specific modes of physical and biological containment, commensurate with the anticipated potential risks, were mandated to minimize the potential harm from an inadvertent release of genetically modified agents. There were also experiments that were forbidden for this reason. At that time, the possibility of state-initiated terrorism was considered but judged to be of lesser concern than accidents.

Although deliberate misuse might well pose a greater risk today, recent calculations suggest that in research with highly transmissible and virulent biological agents, accidental release remains of great concern.§ It is imperative, therefore, that funding agencies and research institutions pay special heed to the effectiveness of the containment being used to minimize the likelihood of either accidental or malicious release. It is also essential that all laboratory personnel be highly trained and tightly supervised to ensure biosecurity.

— Paul Berg

10.1126/science.1229789

\*National Research Council, *Biotechnology Research in an Age of Terrorism* (National Academy Press, Washington, DC, 2004).

†M. Lipsitch *et al.*, *Science* **336**, 1529 (2012). ‡M. Enserink, *Science* **336**, 1494 (2012).

§L. C. Klotz, E. J. Sylvester, *Bulletin of the Atomic Scientists* (7 August 2012); <http://thebulletin.org/web-edition/features/the-unacceptable-risks-of-man-made-pandemic>.

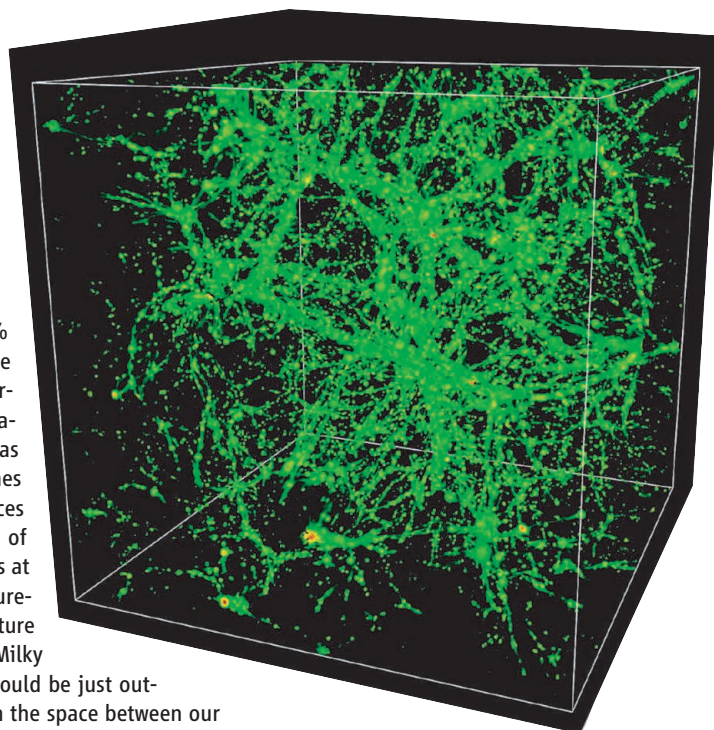


## ASTRONOMY

### Looking for Missing Matter

In the present-day universe, galaxies account for only 10% of baryonic matter (the protons and neutrons that constitute ordinary matter). The rest is expected to be found in the intergalactic medium, mostly in the form of diffuse gas at temperatures ranging from 100,000 to 10 million K. To look for this gas around our galaxy, Gupta *et al.* searched for absorption lines from highly ionized gas in spectra of bright extragalactic sources obtained with the Chandra X-ray Observatory. The detection of both O VII and O VIII absorption lines implies the presence of gas at temperatures around 1 million degrees. Column density measurements combined with emission measurements from the literature indicate that the gas extends over a large region around the Milky Way and is 10 billion times as massive as the Sun. This gas could be just outside the galaxy, in the circumgalactic medium, or anywhere in the space between our galaxy and its closest neighbors. — MJC

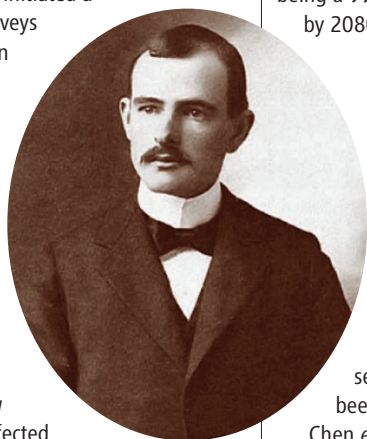
*Astrophys. J.* **756**, L8 (2012).



## ECOLOGY

### Humans Mitigate Climate Change Effects

In the early 20th century, Joseph Grinnell, who cofounded the University of California's Museum of Vertebrate Zoology, initiated a series of biological surveys throughout the western United States. He and his colleagues could not have predicted the extent of climate change that we are experiencing in the 21st century, but their survey data have proven to be invaluable. Morelli *et al.* have used these data to determine how climate change has affected Belding's ground squirrel, a mountain meadow specialist. From resurveys of 74 of the same sites in California's Sierra Nevada Mountains, which were originally sampled between 1902 and 1966, they found that 31 of the ground squirrel populations have been extirpated; in addition, there was no evidence for their having colonized nearby suitable habitats. Next, the authors examined climate, landscape, and land-use data to identify causal factors for the observed range contraction and found that winter cold was the strongest positive predictor of population persistence: Both more frequent rain-on-snow events and a thinner insulating snow



pack are known to harm montane mammals. Interestingly, they found a buffering effect of human activity, such as camping and agriculture, which locally increase food and water availability. Models based on these causal factors predict a continuing contraction of Belding's ground squirrel populations, with the most extreme outcome being a 99% loss of suitable habitat in California by 2080. — SNV

*Proc. R. Soc. London Ser. B.* **279**, 10.1098/rspb.2012.1301 (2012).

## PSYCHOLOGY

### Determinants of Success

As the election races in the United States enter the home stretch, candidates have begun to appear regularly on television broadcasts. Viewer judgments of competence, based on seeing the faces of candidates, have been shown to predict election outcomes. Chen *et al.* have extended this approach to ask whether judgments of candidates' social competence—defined as the capacity for effective functioning in social interactions—are related to outcomes in an individualistic society (the United States) and a collectivist society (Taiwan). They replicate the earlier result that a judgment of competence does predict winners in the United States, as it does in Taiwan, and they find that judgments of social competence are also predictive, though only for elections in Taiwan. Correlating measures of individualism and collectivism from these study participants along with their own voting choices demonstrated that competence was weighted more heavily by more

individualistic voters; similarly, social competence was linked to the choices that collectivist voters made. — GJC

*J. Exp. Soc. Psychol.* **48**, 10.1016/j.jesp.2012.07.006 (2012).

## EDUCATION

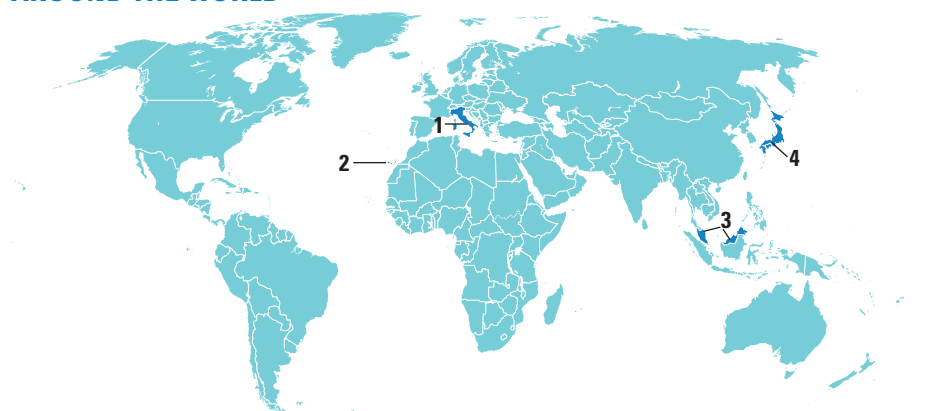
### Sustaining Innovative Teaching

Recent emphasis on improving science education has led to the development of high-quality research-based instructional strategies (RBISs). Henderson *et al.* analyzed the results of a Web survey of U.S. physics faculty in order to better understand the impact of RBISs and to identify any barriers to their use. Results showed that 12% of faculty members are unaware of RBISs, 16% are aware of them but have not tried any, and 23% have tried RBISs but have since discontinued their use. Further analysis indicated that reading education journals, attending workshops focused on teaching, having an interest in RBISs, and being female significantly correlated with knowledge and/or use of RBISs, whereas faculty age, institutional type, percentage of job related to teaching, and large class sizes were not found to be barriers to the use of RBISs. Taken together, these results suggest that although general dissemination strategies and professional development efforts create awareness and motivation to try RBISs, more support, especially related to dealing with student complaints, inability to cover the appropriate amount of content, and weaker-than-promised student outcomes, may be needed for faculty to implement and continue to use RBISs. — MM

*Phys. Rev. ST Phys. Educ. Res.* **8**, 020104 (2012).



## AROUND THE WORLD



## Parma, Italy 1

**Report: Europe's Food Watchdog Is Independent**

The European Food Safety Authority (EFSA) is sufficiently independent from the food industry it oversees, according to an external review issued on 5 September. Lately, EFSA has come under fire from advocacy groups and members of the European Parliament who claimed board members and experts sitting on EFSA scientific panels sometimes have undisclosed ties to industry. But the report, written by auditors from Ernst & Young, says that EFSA has done more to protect the independence of its scientific opinions than required by its founding regulations. It says tightening conflict of interest rules further might make outside experts hesitant to sit on EFSA panels. However, the report recommends that EFSA become more transparent and explain its decisions better to a broader audience.

Critics aren't satisfied. "EFSA's conflict of interest policy has improved, but not enough," says Nina Holland, a campaigner at Corporate Europe Observatory. EFSA's board says it will discuss the findings at its October meeting. [http://scim.ag/\\_EFSA](http://scim.ag/_EFSA)

## Canary Islands 2

**Island Hopping**

Physicists have demonstrated "quantum teleportation" over a distance of 143 kilometers, besting the previous record of 97 kilometers by researchers from China. Instead of making an object disappear in one place and reappear in another, this technique transfers the delicate quantum state of one photon to another photon some distance away. Now, Anton Zeilinger of the University of Vienna and colleagues have teleported the states of

photons between mountaintop observatories on the Canary Islands of La Palma and Tenerife (pictured below), they reported online on 5 September in *Nature*.

"Just showing that you can do it over such very long distances is a major step forward," says Richard Hughes, a physicist at Los Alamos National Laboratory in New Mexico



who was not involved in the work. Rupert Ursin, a member of Zeilinger's team from the Austrian Academy of Sciences in Vienna, says the advance points the way to teleportation between Earth and a satellite and, ultimately, to a quantum-mechanical Internet. The team worked on islands for several reasons, Ursin says, but "the unofficial reason is that the beach is super nice."

## Sabah, Malaysia 3

**Evolutionary Expedition Scales Borneo's Highest Peak**

Following in the footsteps of Alfred Russel Wallace, a contemporary of Charles Darwin, this week 40 Dutch and Malaysian scientists will ascend Borneo's 4000-meter Mount Kinabalu—the tallest peak in Southeast Asia—to study the region's world-famous biodiversity. Menno Schilthuizen of the Naturalis Biodiversity Center in Leiden, the



Netherlands, has spent 7 years documenting unknown species in the region, such as the land snail *Everettia layanglayang* (pictured above). On this expedition, he and his colleagues will spend 2 weeks collecting DNA from plants, animals, and fungi from both the mountaintop and surrounding lowlands with the goal of comparing closely related species from the two environments. They hope to determine which species on Mount Kinabalu are ancient relics from cooler times, and which recently moved from the hot, humid lowlands to the summit's alpine climate. Starting with Wallace, "there is a long history of research on evolution [on the mountain]," Schilthuizen says. "But no one has taken a large-scale approach."

## Kyoto, Japan 4

**Mathematical Gold?**

In 1897, newspaper reports of gold in Alaska triggered a rush of nearly 100,000 adventurers willing to brave an arduous journey and miserable conditions in order to make their fortune. Recent buzz on the Internet may set off something similar, albeit on a smaller, more intellectual scale, in the world of mathematics. For the last few years, Shinichi Mochizuki of Kyoto University in Japan has issued progress reports on a new field of mathematics that he has been developing called Inter-universal Teichmüller theory. His fourth report, posted at the end of August, stakes a claim to a potential gold mine: Mochizuki announced he has solved a famous problem in number theory called the abc conjecture.

The abc conjecture is concerned with solutions to the seemingly trivial equation  $a + b = c$ . The technicalities involved in the conjecture's precise statement are familiar ones, number theorists note. But Mochizuki's theory is based on very new, highly technical math explored so far only by a very few. If initial assessments of Mochizuki's claim hold up, there'll be an influx of mathematical prospectors primed to use his proof to mine their own intellectual gold.

[http://scim.ag/\\_conjecture](http://scim.ag/_conjecture)

## NEWSMAKERS

## New Leader for SKA

**Philip Diamond**, a British astronomer working in Australia, has landed perhaps the biggest job in astronomy: leading the design and preparing for construction of a €1.5 billion radio telescope that comprises thousands of dishes and spans two continents.



Diamond

The Square Kilometre Array (SKA) aims to peer back in time to the universe's earliest stars and galaxies, study gravity, and look for signs of extraterrestrial life. The task requires dishes spread over continental distances with a combined collecting area of 1 square kilometer. Project leaders recently decided to split the array between two sites, centered in Australia and South Africa, each handling different frequencies (*Science*, 1 June, p. 1085). The plan is to start building the array in 2016 and finish by 2024.

Diamond has held senior positions at astronomy organizations in the United Kingdom, Sweden, Germany, and the United States and is currently head of astronomy and space science at Australia's research organization CSIRO. He is also a longtime member of SKA's scientific steering committee. "He's an excellent choice," says Michael Garrett, director of ASTRON, the Netherlands Institute for Radio Astronomy.

## Golden Goose Awards Celebrate Basic Research

What do lasers, coral, and glowing jellyfish have in common? Research on these initially obscure subjects eventually led to important scientific advances in technology and health, including two Nobel Prizes. On 13 September, the scientists whose basic research paved the way for useful products and techniques—including laser technology, safe bone grafts, and green fluorescent protein—will receive the first Golden Goose Awards. Organized by U.S. Representative Jim Cooper (D-TN) and a coalition of leaders in education, business, and science, including AAAS (the publisher of *Science*), the awards are a playful rejoinder to those who criticize basic research as a waste of money. At first, recipient **Martin Chalfie** of Columbia University thought the Golden Goose Award "was a hoax." But Chalfie, who shared the 2008 Nobel Prize

in chemistry for developing green fluorescent protein from bioluminescent jellyfish, says he's delighted to receive the prize. He hopes the awards will serve as a reminder that many of the biggest discoveries in science are joyful surprises. "We shouldn't be so narrow in our seeking."

[http://scim.ag/\\_goose](http://scim.ag/_goose)

## Lasker Awards for Molecular Motors, Liver Transplantation

This year's Lasker Awards go to researchers whose work unraveled how molecular motors work and others who made liver transplants possible.

**Michael Sheetz** of Columbia University, **James Spudich** of Stanford University, and

**Ronald Vale** of the University of California, San Francisco, won for basic medical research. They used in vitro assays to discover how cytoskeletal motor proteins move material within cells. The motors also allow cells to move and muscles to contract.

**Roy Calne** of the University of Cambridge and **Thomas Starzl** of the University of Pittsburgh will receive the Lasker clinical award for their studies of liver transplantation. Working first with dogs, they developed strategies surgeons could use to deal with the liver's complex system of blood vessels and with immune system rejection. In 1983, liver transplantation became an accepted medical procedure.

A third prize for special achievement in medical science goes to geneticists >>



## All That Glitters

This tiny, iridescent African fruit may look delectable, but don't be fooled. It's neither tasty nor nourishing and contains no pigments to extract. Instead, the vivid sparkle of *Pollia condensata* comes from the interaction of light with the fruit's skin, which contains layers of microscopic, rod-shaped cellulose fibers. Stacked like spiral staircases, the rods are spaced at slightly different intervals, which reflect different colors. Most reflect blue light, while others reflect different parts of the visible spectrum, producing a rainbow. The overall effect is a metallic blue brighter than any blue yet described for a biological material, researchers reported online on 10 September in the *Proceedings of the National Academy of Sciences*. The fruit's dazzling display may have evolved to capitalize on birds' attraction to sparkly objects, says biologist Beverley Glover of the University of Cambridge in the United Kingdom, or to trick them into eating something that looks like a blueberry without going to the trouble of actually making juicy flesh. <http://scim.ag/bluefruit>



## Random Sample

## Reality TV: Not Just a Guilty Pleasure

Even the most ardent fans of reality TV don't claim that it's educational. But the Massachusetts Institute of Technology (MIT) in Cambridge might be about to change that. A new online video series called ChemLab Boot Camp follows 14 first-year MIT students as they navigate course 5.301, Chemistry Laboratory Techniques. The series covers their first fumbling interactions with beakers and burettes as they attempt to master techniques such as column chromatography and vacuum distillation. The 2- to 5-minute episodes blend fly-on-the-wall footage with animated explanations of lab techniques that the students attempt. The goal, says George Zaidan, an MIT alumnus who produced and directed the 14-episode series, is to get more high-school students interested in majoring in science, technology, engineering, and math. But will the idea of university courses as boot camp scare away budding scientists? Zaidan doesn't think so. "On the first day you don't know the difference between an Erlenmeyer flask and a graduated cylinder," he says. "But over time things that seemed really scary become second nature, so that's part of the message." The series premieres on 18 September and is accessible via MIT OpenCourseWare (<http://ocw.mit.edu/high-school/chemistry/chemistry-lab-boot-camp>).



## &gt;&gt; NEWSMAKERS

**Donald Brown** of the Carnegie Institution for Science in Baltimore and **Tom Maniatis** of Columbia University. The two are honored for their research and leadership in promoting technology and supporting young scientists.

The awards from the Albert and Mary Lasker Foundation, to be presented on 21 September in New York City, include a \$250,000 honorarium. <http://scim.ag/Lasker2012>

## Scientists Win 'Enormous' Balzan Prize

The Milan, Italy-based International Balzan Prize Foundation—which annually funds research awards for scholars, scientists, and artists whom it considers to have been overlooked by other prestigious awards—announced this week that two scientists will each receive the CHF \$750,000 (approximately \$790,000) Balzan Prize. The committee awarded the solid earth sciences prize to geophysicist **Kurt Lambeck** of the Australian National University in Canberra for his work on the interplay among glacial melting, sea-level change, and rising landmass resulting

from climate change.

Geneticist **David Baulcombe** of the University of Cambridge in the United Kingdom received the prize for epigenetics for his work on the epigenetic effects of stress on plant cells and tissue. Baulcombe says the "enormous" prize will help start a new line of epigenetic research into algae. "It's a good enough life getting to be a scientist," he says, "and this is just icing on the cake."

## FINDINGS

## Facebook Friends Influence Voting

There's no doubt that our Facebook friends influence how we spend our time on the Internet. But how much does social media influence our real-world behaviors once we step away from the computer? A lot, according to an experiment performed on 60 million Facebook users.

Less than 40% of eligible U.S. voters usually take part in congressional elections. As a public service in 2010, Facebook rolled out a nonpartisan "get out the vote" campaign during the 2010 congressional elections that appeared on every user's newsfeed. A team led by political scientist

## BY THE NUMBERS

**20 billion tons** Annual loss of ice from the Southern Patagonian Ice Field, according to an analysis published on 5 September in *Geophysical Research Letters*. That is about 9000 times the volume of water stored annually by the Hoover Dam.

**10 million to 20 million cubic meters** Increase in the volume of molten rock beneath Santorini's volcano between January 2011 and April 2012, raising the Greek island's surface by 8 to 14 centimeters, according to a study published on 9 September in *Nature Geoscience*.

**\$30 million** Amount donated by the National Football League for brain injury research at the National Institutes of Health, announced on 5 September.

Robert Bond at the University of California, San Diego, turned that campaign into a massive controlled experiment. Sixty million people who logged in to Facebook on a single day were shown a message that encouraged them to vote, including links to local polling stations and a clickable "I Voted" button. Some messages also included pictures of Facebook friends who had already voted. Researchers then compared the number of people reporting on Facebook that they voted with official voting rolls after the election.

People who received messages alerting them that their friends had voted were 0.39% more likely to vote than those who received messages with no social information. That translates to an additional 282,000 votes cast, the team reports online on 12 September in *Nature*.

## Science LIVE

Join us on Thursday, 20 September, 3 p.m. EDT for a live chat with experts on **whether a restricted diet prolongs life**. <http://scim.ag/science-live>





**Keep out.** Afghan soldiers protect a copper mine—and ancient Buddhist relics—from the Taliban.

## ARCHAEOLOGY

# Time Ticks Away for Ancient Afghan Monasteries

Last month, Taliban-launched rockets landed just a few hundred meters from a unique complex of 1500-year-old Buddhist monasteries. That incident came on the heels of a land mine accident that severely injured two Afghans working on the multinational team excavating the site. But many archaeologists say the greatest threat to the sprawling collection of stupas, workshops, and temples comes not from the Taliban but from the Western-backed government: It intends to order the team to withdraw from the central part of the site at the end of the year so that Chinese miners can begin tapping a rich vein of copper that sits beneath the ancient statues and paintings. Archaeologists are lobbying for more time, noting that mining efforts are not likely to begin for more than a year.

The \$3.5 billion contract between the Afghanistan government and China Metallurgical Group Corp., signed in 2007, is the country's largest and could provide desperately needed revenue for this struggling country. But after an international outcry over plans to dynamite the monasteries, archaeologists at the place called Mes Aynak, just south of Kabul, were given 3 years starting in 2009 to complete their investigations (*Science*, 4 March 2011, p. 1124). The effort, however, has been plagued with delays,

infighting, and security concerns. Outside archaeologists say the team has done its best under very difficult circumstances but fear that critical data will be lost when the archaeologists leave and the area is destroyed for the mine. "It would be of great historical value not only for the history of Afghanistan but the whole region if they could slow down, excavate, and document properly," says Deborah Klimburg-Salter, a University of Vienna archaeologist.

The archaeology project, funded with \$8 million from the World Bank and overseen by the Afghan Ministry of Mines, has uncovered a vast array of buildings filled with more than 1000 statues, many religious texts, and rare wooden ornamentation, offering an unprecedented glimpse into the social and economic life of ancient monks, miners, and artisans who themselves used the high-quality copper ore. "This will completely revise our understanding of Buddhism in the region," says Philippe Marquis, the director of the French archaeological mission in Afghanistan. Jonathan Mark Kenoyer, an archaeologist at the University of Wisconsin, Madison, who visited Mes Aynak last month, agrees. "This is a very important site full of stupas and slag; it was fortified and industrial," he says. "It blew me away."

Marquis and Omar Sultan, an archaeolo-

gist and former Afghan deputy minister of culture, insist that much of the central area has been excavated, and that work there should be completed on schedule by the end of the year. Others disagree, arguing that the team has been able to conduct only the most basic salvage work, such as removing statues for conservation. Under the current approach, says former site coordinator Hans Curvers, "the art historians will be happy with more statues and paintings, and we don't know anything about the context they came from." Kenoyer echoes that concern. "They're not finished," he says. "Just last week they found 16 new stupas. ... And they haven't even begun to investigate the most important period—the prehistoric era." He suspects that Mes Aynak or nearby mines might have supplied the Indus River civilization to the south with copper as early as 2000 B.C.E.

The clash between the country's ancient heritage and future needs has been exacerbated by bureaucratic tangles. For example, Curvers, a Dutch archaeologist, was hired last year on a 1-year contract to coordinate the archaeology. But after sending a series of memos complaining about issues such as slow payment of workers' wages, he was fired in February and replaced with a British contract archaeologist. (Kenoyer confirms that during his visit, upset workers were slow to be paid.) Curvers's dismissal letter from Min-



**Head hunters.** Archaeologists found more than 1000 sculptures, including this 1500-year-old head.

istry of Mines official Waheedullah Qaderi accused him of making the situation "more complex" by communicating with those outside the ministry. Qaderi did not reply to

requests for comment.

Marquis acknowledges that the work got off to a slow start and has been hobbled by complications. “Only in the last 4 months have we gotten all the equipment we need,” he notes. “We’ve had no choice but to do rescue excavations.” He hopes that the ministry will agree to extend the 1 January 2013 cutoff date. “It is obvious to everybody that mining is not going to start for a year or maybe two,” he says. “So we’re hoping they will give the archaeologists more time.”

Cheryl Benard, founder of the Washington, D.C.-based Alliance for the Restoration

of Cultural Heritage, worries that the ministry wants to shut out archaeologists and media. “Then the site will be their own private little encampment where they can do whatever they want,” she says.

Marquis, however, says that more than half of the ruins lie outside the central zone, although within the heavily guarded perimeter, and will still be accessible. An additional \$4 million in World Bank money is set aside for further digs, he adds. Brendan Cassar, the U.N. heritage representative in Kabul, adds that he hopes mining and archaeology could coexist at the site.

But the August rocket attacks on the Chinese compound in the central zone led Chinese workers to abandon the site. The nightmare scenario, Marquis and Kenoyer say, is that the company temporarily stops paying for security, including some 2000 Afghan guards currently employed. Then Mes Aynak likely would be overrun with illegal diggers seeking the many beautiful objects highly valued in the art market. “If there’s no mining, it will be looted,” Marquis says. “And if there is mining, it will be destroyed. The one thing we know for sure is that this site is doomed.”

—ANDREW LAWLER

## MASS EXTINCTIONS

# Before the Dinosaurs’ Demise, a Clambake Extinction?

Most researchers think the dinosaurs, many plants on land, and much of the life in the sea succumbed to a huge cosmic impact 65.5 million years ago. But new evidence from the sea floor just off Antarctica points to a major extinction there a geologic moment before the impact. The culprit in this earlier cataclysm may well have been humongous volcanic eruptions in India—the same eruptions that some researchers have credited with wiping out the dinosaurs.

Nailing down what killed the dinosaurs and the 65% of other species that disappeared with them has been a matter of timing. The impact left a layer of distinctive debris around the world, a perfect marker for paleontologists trying to connect the impact to extinctions recorded in the same sediments.

In the fossil record of ocean sediments, microscopic plants and animals disappeared in the same geologic instant that the impact debris was laid down, clinching the case that the impact caused the ocean extinction. On land, abundant plant pollen and leaves built a similarly strong case. As to the land-dwelling dinosaurs and mammals, their less-abundant fossil record made their case less airtight, but most researchers still consider it proven beyond a reasonable doubt.

But there were still the Indian eruptions. Their outpourings formed the Deccan Traps, a pile of lava as voluminous as the Siberian Traps that formed 252 million years ago or the magmatic gushings left when the Atlantic Ocean began opening 200 million years ago. Noxious, climate-altering emissions from the latter two eruptions are tentatively credited with triggering two other mass extinctions. But any extinctions due to the Deccan eruptions have been indistinguishable from those of the impact.



**Survivor.** Warming may have killed off clams as free-swimming ammonites, such as this one, escaped.

So paleontologists Thomas Tobin and Peter Ward of the University of Washington, Seattle, and colleagues went where they thought they’d have the best chance of separating any second extinction from the impact mass extinction: Seymour Island just off the Antarctic Peninsula. At such a high latitude, any warming from the Deccan’s greenhouse gas emissions would have been greatly amplified, they reasoned. And sediment had accumulated so rapidly on the ancient sea floor there that the fossil record was stretched out, in effect enlarging the typeface that paleontologists had been straining to read.

After applying two analytical tools to the Seymour Island record for the first time, Tobin and his colleagues argue in the 15 September issue of *Palaeogeography, Palaeoclimatology, Palaeoecology* that the Deccan erup-

tions caused a significant extinction that took place before the impact. A key was getting the timing right. They determined when Earth’s magnetic field had flip-flopped by measuring the field’s orientation preserved in Seymour Island sediment. Comparing the results with the Deccan paleomagnetic record, the researchers determined when in the Seymour Island record Deccan eruptions had occurred. Measurements of the oxygen-isotope composition of carbonate fossils throughout the Seymour Island record showed a sharp 7°C warming of bottom waters. And a reanalysis of the Seymour Island fossil record revealed the sudden extinction of about 40% of bottom-dwelling clams and snails.

Taken together, Tobin and colleagues say, those events tell a story: About 200,000 years before the impact, a series of major Deccan eruptions began. At the same time, bottom waters began warming off the coast of Antarctica. About 40,000 years later, well before the impact, the clams and snails were going extinct off Antarctica. The timing is right, they say, and the physical links from eruption emissions to greenhouse warming to extinction by overheating is plausible.

They may even be right. “It’s great work,” says paleontologist Kirk Johnson of the Denver Museum of Nature & Science. “This is a really nice additional data set. It’s just that I’ve grown really cautious about correlating things. You have to show things happen at the same time, and that’s challenging in this time period.” Johnson worries most about the relatively poor dating of the Deccan paleomagnetic record back in India, but says he hopes more research along the proposed thousands-of-kilometers-long chain of causation will help settle what really happened.

—RICHARD A. KERR



## GM RESEARCH

# Charges Fly, Confusion Reigns Over Golden Rice Study in Chinese Children

**SHANGHAI, CHINA**—A U.S.-funded study in which Chinese schoolchildren were fed genetically modified (GM) rice 4 years ago has triggered a firestorm in the Chinese media. Newspaper columnists accused the main authors, both of Tufts University in Boston, of using children as “guinea pigs”; some stories likened the study to Japanese biowarfare experiments on Chinese prisoners in World War II. The furor has prompted several Chinese collaborators on the study to distance themselves from the work, and one of them was suspended.

The criticism targets a trial of golden rice, a controversial crop developed to fight vitamin A deficiency (*Science*, 25 April 2008, p. 468). The results of the trial, funded by the U.S. National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK) and the U.S. Department of Agriculture (USDA), were published online to little notice by *The American Journal of Clinical Nutrition* on 1 August. But on 29 August, Greenpeace China claimed in a press release that the study had violated a Chinese government “decision to abort plans for the trial,” which it called “a scandal of international proportions.”

The group offered little evidence to support its allegations, but in a 5 September statement, Tufts University said it is “deeply concerned” and is conducting a “thorough review.” Pending the outcome, an interview with the paper’s first author, Guangwen Tang, would be “not appropriate,” a spokesperson says. (Tang is a Chinese-born researcher at a USDA-funded nutrition lab at Tufts.) The paper’s last author, renowned nutrition scientist Robert Russell, was out earlier this week due to family circumstances.

The study had come under fire before. In 2008, the advocacy group GM Free Cymru (Wales) sounded the alarm, and 22 researchers decried the study as a breach of medical ethics in an open letter to Russell, arguing that golden rice was unsafe to eat. In a 2009 letter, an NIDDK communication officer said the study had been approved by ethical panels at Tufts and the Chinese Academy of Preventive Medicine, that there were “many safeguards” to protect participants, and that the U.S. Department of State had cleared the trial after

a review for “any potentially negative foreign policy implications.”

By that time, the trial was already finished, says Adrian Dubock, manager of the Golden Rice Project in Dornach, Switzerland. (While not involved in the study, Dubock says he has followed it closely.) But Greenpeace says it had assumed the Chinese government halted the trial in 2008, citing an



**Scary science.** A cartoon from news agency Xinhua shows a U.S. researcher feeding genetically modified rice to a Chinese child.

e-mail from that year from an official in the Chinese agriculture ministry’s GMO Biological Safety Administration Office. The e-mail said the Zhejiang Provincial Department of Agriculture had been instructed to ask the Zhejiang Academy of Medical Sciences to stop the study. The ministry’s office did not respond to interview requests.

Golden rice was created in the 1990s as an attempt to help people worldwide suffering from vitamin A deficiency, which is estimated to cause blindness in more than a quarter of a million children annually. By making rice produce  $\beta$ -carotene, a precursor to vitamin A, researchers hoped to solve that problem in countries where rice is a staple.

The study in China sought to find out how efficiently  $\beta$ -carotene from golden rice is converted to vitamin A once it’s ingested. To be relevant, Dubock says, the trial had to be done in a rice-growing country and in children, who are most vulnerable to vitamin A shortages. According to the published study, the researchers fed 72 children either golden rice, spinach, or capsules with  $\beta$ -carotene in oil.

They reported that golden rice was as good a vitamin source as the capsules and better than spinach—a “fantastic result,” Dubock says, because it means modest amounts of rice will provide benefits.

In the wake of the uproar, the Chinese co-authors have denied their involvement. On 5 September, the state-run *People’s Daily* quoted Hu Yuming, a researcher at the Hunan Center for Disease Control and Prevention, as saying he was “completely baffled” as to why his name appeared on the paper. “I am unaware of that paper,” another co-author, Wang Yin of the Zhejiang Academy of Medical Sciences, reportedly told the same newspaper. (Neither could be reached for comment by *Science*.)

The Chinese Center for Disease Control and Prevention (Chinese CDC), however, confirmed that the Chinese researchers, including the CDC’s Yin Shi’an, collaborated with Tang, but stated that they only gave the students spinach and capsules; the golden rice part was a Tufts project of which Yin had been unaware, the statement suggested. Nonetheless, the CDC suspended Yin for “inconsistencies” in his story.

The Chinese CDC account contradicts that of the Zhejiang Academy of Medical Sciences, which on 7 September said that Yin was listed as a principal investigator, with the academy’s Wang, on an agreement the academy signed with Tufts in 2004 to research golden rice. (Yin declined to be interviewed.)

Dubock says he has received information that the Chinese researchers had been “intimidated” by home visits from police. “Of course they knew” that golden rice was being tested, he says. He calls Greenpeace’s actions “callous and cynical” and says there’s a “xenophobic” element to the outrage. One cartoon on the website of state news agency Xinhua showed a curly-haired scientist wearing a tie emblazoned with the American flag, staring through a microscope while dropping unnaturally colored kernels of rice into a Chinese child’s mouth.

China’s leaders are generally supportive of GM crop research (*Science*, 5 September 2008, p. 1279). The new controversy could mean “short-term adverse effects,” says Huang Jikun, director of the Chinese Academy of Sciences’ Center for Chinese Agricultural Policy in Beijing. But ultimately, he says, “China’s GM technology will continue to develop as the nation has planned.”

—MARA HVISTENDAHL AND MARTIN ENSERINK



## SCIENTIFIC MISCONDUCT

# Government Sanctions Harvard Psychologist

In 2010, Harvard University psychologist Marc Hauser seemed to be at the pinnacle of his career. His provocative work probing the biological origins of cognition and morality had yielded collaborations with prominent scholars, as well as frequent media attention. And with the recent publication of a popular book on moral cognition, he had moved into the rarified sphere of the public intellectual.

Then a Harvard investigation concluded that the author of *Moral Minds: How Nature Designed Our Universal Sense of Right and Wrong* had engaged in scientific misconduct. Last week, the U.S. Department of Health and Human Services Office of Research Integrity (ORI) confirmed the findings, revealing that Hauser fabricated and falsified methods and data in six federally funded studies.

The news brought closure to those who questioned whether Hauser was guilty of any wrongdoing. But because neither investigation indicates which of Hauser's hundreds of publications were investigated, many researchers remain uncertain about how to regard the rest of his work. "Many of my colleagues are reluctant to cite certain work that came out of Hauser's lab," says Yale University experimental philosopher Joshua Knobe.

Hauser, who resigned from Harvard in 2011, wrote in a statement that although he has "fundamental differences" with some of the new report's findings, "I acknowledge that I made mistakes." He did not admit deliberate misconduct, however, and implied that his mistake was that he "tried to do too much" and "let important details get away from my control."

"It is sad that Hauser still will not admit to the charges that have been found against him when he does appear to nonetheless accept that the evidence exists and is legitimate," Gerry Altmann wrote in an e-mail to *Science*. A psychologist at the University of York in the United Kingdom, Altmann is editor of *Cognition*, one of the journals that retracted some of Hauser's research.

Hauser's work first fell under suspicion in 2007, when members of his laboratory brought concerns to Harvard officials, instigating a 3-year internal investigation. In August 2010, *The Boston Globe* broke the news that the Harvard investigation had found Hauser "solely responsible" for eight instances of scientific misconduct and that Hauser was taking a year's academic leave. In July 2011, he resigned his position.

In the report released last week, ORI iden-

tified six instances in which it concluded that Hauser engaged in research misconduct in studies funded by the U.S. National Institutes of Health. Specifically:

- In a study of learning in cotton-top tamarins published in the journal *Cognition* in 2002 and retracted in 2010, Hauser published fabricated data in a bar graph that ostensibly compared the monkeys' responses before and after they habituated to sound patterns.

- In two unpublished experiments testing cotton-top tamarins' responses to strings of consonants and vowels, Hauser recorded false values for some of the monkeys' responses, creating the appearance of statistically significant results.

- In versions of a manuscript for a study that was published in *Cognition* (but first submitted to and rejected by other journals, including *Science*), Hauser provided false descriptions of the methods used to code monkey behavior and falsified results in a way that supported his theoretical predictions. Hauser and his collaborators corrected these problems, so the published study accurately describes the research.

- In a study of how well rhesus monkeys comprehend human gestures, published in the *Proceedings of the Royal Society B* in 2007, Hauser falsely reported methods and results of one of seven experiments. Hauser and one of his colleagues published a replication of this experiment in 2011.

- A 2007 *Science* paper contained a false statement about distinctive markings on some cotton-top tamarins in the experiment, masking the possibility that some monkeys could have been tested more than once. Hauser accepted responsibility for this statement. He and a co-author replicated these findings in a 2011 *Science* paper.

- In an experiment involving rhesus monkeys that was never written up for publication, Hauser falsely changed coding results.

The ORI report states that Hauser "neither admits nor denies committing research misconduct but accepts ORI has found evidence of research misconduct." For the next 3 years, any research he conducts using U.S. Public Health Service (PHS) funds must be done under supervision and must be certified as legitimate by the institution that

employs him. He also cannot serve as a peer reviewer or in any other advisory capacity to PHS during that period.

Some scientists who have defended Hauser continue to do so. Psychologist Bennett Galef of McMaster University in Hamilton, Canada, reviewed the evidence for some of the charges against Hauser during Harvard's investigation at Hauser's lawyers' request. He says he saw no clear evidence of wrongdoing then and remains unconvinced, especially by evidence of misconduct in studies that are unpublished. "It's conceivable, after all, that someone would feel tempted to do something with their data and then realize what they'd done and say, 'That was a mistake and I just won't publish it,'" Galef says.



**Better days.** A federal investigation concluded that Marc Hauser engaged in research misconduct.

"How can you get somebody in such trouble over something that they didn't publish?"

Other scientists vehemently disagree. In an e-mail to *Science*, Altmann wrote: "Even if the ONLY transgression was the fabrication in *Cognition*, the field would consider that totally unacceptable and reprehensible behavior. The fact that he has misled collaborators in unpublished studies shows that this is a recurring pattern of behavior."

Several of Hauser's former co-workers privately expressed sympathy for his ordeal. But others' sympathies lie elsewhere. "The thing I find especially tragic," Knobe says, "is that the whistleblowers themselves—who were the moral heroes in this situation—their own work is now falling under a cloud of suspicion because they were doing work with Marc."

—SIRI CARPENTER

Siri Carpenter is a freelance writer based in Madison.

## U.S. ELECTIONS

# In a Torrent of Campaign Rhetoric, Hints of Science Policy

They may not move many voters, but science and technology issues are starting to get some attention in the U.S. presidential campaign.

In the past few weeks, both the Republican and Democratic parties have released lengthy platforms that offer insights into their views on a range of research-related matters, from climate change to biomedical studies. The two presidential contenders, President Barack Obama and former Massachusetts governor Mitt Romney, have set out positions on thorny challenges such as returning American astronauts to space and enabling foreign-born scientists to work and live in the United States. They've also answered 14 questions posed by a coalition of pro-science organizations, including AAAS, which publishes *Science* (ScienceDebate.org).

Taken together, the election-season outpouring reveals some striking differences between the two candidates, as well as how their parties have shifted since 2008. There are also some broad areas of agreement (see platform statements, below and opposite page). But observers caution voters not to get too carried away with the rhetoric on either side. "There isn't a party or candidate in history that has been able to fully implement their vision—and few expect to," says political scientist Quentin Kidd of Christopher Newport University in Newport News, Virginia. Party platforms in particular, he notes, are "aspirational" documents designed to give voice to an array of party constituencies. In addition, presidential candidates often hold positions at odds with their own party's plank. Still, "words do matter," he says, noting that the rhetorical posturing can "help reveal how [candidates and

parties] view the role of science in solving problems and making policy."

Voters looking for hints on how a second Obama Administration or a rookie Romney team might govern now have plenty of raw material. Among the highlights:

**A bipartisan cheer for biomedical science, but a split on stem cell studies.** In the 2012 platforms, both parties promise to sustain—and even beef up—federal spending on basic biomedical research. But don't look for details, including their plans for the National Institutes of Health, the field's major funder. "[W]e will continue to support America's groundbreaking biomedical researchers in their lifesaving work," vows the Democratic platform. The Republican edition goes a step further, singling out "the neuroscience research that may hold great potential for dealing with diseases and disorders such as Autism, Alzheimer's, and Parkinson's." Both platforms also heap praise on a global health program created under President George W. Bush—the President's Emergency Plan for AIDS Relief, which now provides aid to more than 30 nations.

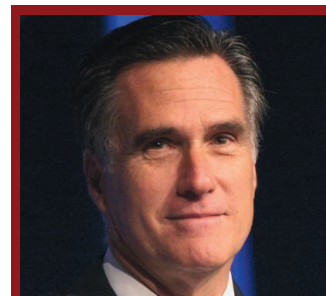
Stem cell research remains a divisive issue, however. The Democratic platform lauds a March 2009 executive order from Obama lifting certain restrictions on federally funded research involving human embryonic stem cells. In contrast, the Republican platform opposes "the killing of embryos for their stem cells" and any federal funding for the field. Instead, it urges expanded government funding for studies using "adult stem cells, umbilical cord blood, and cells reprogrammed into pluripotent stem cells."

**Shared retreat on climate, but still a deep divide.** In 2008, both platforms devoted a

lot of ink to how the federal government should address climate change, as did then-candidate Obama and his Republican opponent, Arizona Senator John McCain. This year, however, the issue essentially disappears from the Republican platform, and the Democratic edition retreats from earlier promises to pass "cap and trade" legislation to cut U.S. emissions of greenhouse gases and negotiate a "binding and enforceable" international agreement to curb global warming. On the campaign trail, Romney and Obama have clashed over the uncertainty surrounding climate science—and what it means for policy.

"[T]here remains a lack of scientific consensus on the issue—on the extent of the warming, the extent of the human contribution, and the severity of the risk—and I believe we must support continued debate and investigation within the scientific community," Romney wrote in his response to ScienceDebate. But the United States shouldn't regulate emissions, Romney added, unless other major emitters take similar steps. The Republican platform urges Congress to "take quick action" to prevent the Environmental Protection Agency from regulating greenhouse gas emissions.

The Democratic platform takes a slap at such ideas. It calls climate change "one of the biggest threats of this generation" and asserts: "Our opponents have moved so far to the right as to doubt the science of climate change." Obama took direct aim at his climate critics in his 6 September nomination acceptance speech to the Democratic National Convention in Charlotte, North Carolina, saying that "climate change is not a hoax." But the platform offers no new policy prescriptions, instead pledging to work "toward an agreement to set emission limits in unison with other emerging powers."



REPUBLICANS

## ON CLIMATE

"The current Administration's most recent National Security Strategy ... elevates 'climate change' to the level of a 'severe threat' equivalent to foreign aggression. The word 'climate,' in fact, appears in the current President's strategy more often than Al Qaeda, nuclear proliferation, radical Islam, or weapons of mass destruction."

## ON IMMIGRATION

"We can accelerate the process of restoring our domestic economy ... by a policy of strategic immigration. ... [F]oreign students who graduate from an American university with an advanced degree in science, technology, engineering or math should be encouraged to remain here."



**Lost in space?** Both candidates “have pretty much punted on making space policy an issue,” says John Logsdon, a space policy analyst at George Washington University in Washington, D.C., and their platforms reflect that ambivalence. The Democratic platform says tersely that Obama has “charted a new mission for NASA,” but doesn’t delve into his decision to cancel Bush-era plans to return astronauts to the moon or his proposed cuts in robotic missions to Mars. The Republican platform is similarly vague—calling only for “launching more science missions” to maintain U.S. pre-eminence in space. Romney told ScienceDebate that, if elected, he will convene a blue-ribbon panel to develop a road map for NASA’s human and robotic programs.

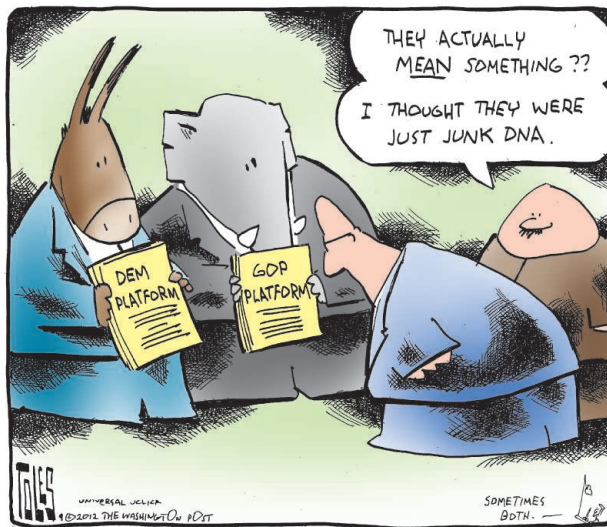
### All in on energy, but diverging priorities.

Both the Obama and Romney campaigns say they have an “all of the above” strategy for developing energy sources. That phrase conveys support for the development of fossil, nuclear, and renewable energy supplies. But that doesn’t mean their priorities are identical. Democrats tend to emphasize the need to improve energy efficiency, develop “clean energy” sources such as solar and wind power, and protect sensitive ecosystems. The Democratic platform, for instance, promises to bar oil and gas drilling in Alaska’s Arctic National Wildlife Refuge and vast swaths of coastal waters. The Republican platform, in contrast, calls for opening those areas to development in order to take “advantage of all our American God-given resources.”

The two parties also clash over how much the government should help companies develop new technologies. The Obama Administration has provided taxpayer-backed loans and other incentives for companies attempting to commercialize solar

and wind technologies, sometimes losing hundreds of millions of dollars when the companies failed. The Republican platform slams that approach, stating that “taxpayers should not serve as venture capitalists for risky endeavors” and promising that a Romney Administration “will not pick winners and losers in the energy marketplace.”

There is one government energy program that both campaigns have hailed, however: The U.S. Department of Energy’s Advanced Research Projects Agency—



Energy (ARPA-E). The 3-year-old agency provides research funds (but not business capital) to companies involved in developing “high-risk,” early-stage energy technologies. The ARPA-E approach “holds the most potential for achieving significant advances in the energy sector,” the Romney campaign said in a 23 August white paper. And both campaigns support making permanent a research and development tax credit that allows businesses to deduct research expenses. (Congress currently renews the credit annually because it has not identified a permanent funding mechanism to offset the lost revenue.)

### A vague view on immigrant scientists.

Both 2012 platforms give more attention than they did in 2008 to the fate of foreign-born students who earn advanced degrees in science and engineering fields from U.S. universities. Each highlights the importance of keeping this technical talent in the country, but both stop short of backing the idea of automatically giving such graduates the right to stay and work in the United States. Both Romney and Obama have embraced the idea in speeches, but the Republican-controlled House of Representatives is wary of that approach.

### A warning against politicized science.

In 2008, it was the Democratic platform that decried the Bush Administration’s politicization of science, charging that it had suppressed unpopular findings and played up those that supported its policies. This year, it’s the Republican platform’s turn to accuse the sitting government of skewing science. In a section on environmental policy, for example, it states: “We must restore scientific integrity to our public research institutions and remove political incentives from publicly funded research,” although it offers no specific examples.

**Silence on the budget.** One topic conspicuous for its absence is how the \$160 billion federal research budget will fare in the debate over how to trim the massive federal deficit. Neither candidate has specifically addressed which research agencies would feel the biggest pinch if federal spending grows more slowly, or goes into reverse, over the next decade. So voters will have to form their own opinions as they head to the polls on 6 November—and then watch what happens in 2013.

—DAVID MALAKOFF

With reporting by Meghna Sachdev.



DEMOCRATS

### ON CLIMATE

“We know that global climate change is one of the biggest threats of this generation. ... We affirm the science of climate change, commit to significantly reducing the pollution that causes climate change.”

### ON IMMIGRATION

“To make this country a destination for global talent and ingenuity, ... we will work to make it possible for foreign students earning advanced degrees in science, technology, engineering, and mathematics to stay and help create jobs here at home.”

# Who Invented the Higgs Boson?

**Five living theorists have claims to having dreamed up the most famous subatomic particle in physics. But what did they really do?**

**NOW THAT THE HIGGS BOSON**—OR something much like it—is in the bag, the question on many people's minds is who gets the Nobel Prize for the discovery.

If you go by the pop history, the answer is obvious. In 1964, Peter Higgs, a mild-mannered theorist from the University of Edinburgh in the United Kingdom, dreamed up the particle to explain the origins of mass. He completed physicists' standard model of fundamental particles and forces. Experimenters working with the world's largest atom smasher, the Large Hadron Collider (LHC) at the European particle physics laboratory, CERN, in Switzerland, have now seen that particle (*Science*, 13 July, p. 141). So Higgs gets the glory.

Only that's not exactly what happened. In fact, theorists say, Higgs made a fairly narrow and esoteric advance in mathematical physics. Several other physicists made the same advance at the same time. Their intellectual leap was essential to the development of the standard model, perhaps the most elaborate and precise theory in all of science. But their papers didn't even mention the most important problem their work helped to solve. Other scientists did that later—but their contribution (which won Nobel laurels in 1979) still doesn't explain the origins of all mass.

Even the famous particle, the Higgs boson, doesn't quite live up to its legendary status. Often portrayed as the engine that drives the

standard model, the Higgs boson itself is in a way the byproduct of more important underlying physics. Instead of the boiler on a steam locomotive, it's more like the whistle: Its toot proves that the boiler is there and working, but it doesn't turn the wheels.

As for whether the work of Higgs and colleagues merits a Nobel Prize, opinions vary. "Certainly, yes, I think it is at least as profound as other things that have been given the Nobel in the past," says Frank Close, a theorist at the University of Oxford in the United

Kingdom. Others question whether the advance was a big enough step beyond previous work to merit science's biggest prize.

In any case, says Chris Quigg, a theorist at Fermi National Accelerator Laboratory (Fermilab) in Batavia, Illinois, historians and prize committees must be careful to give credit precisely where and for what it is due: "If these people receive their rewards, either in heaven or before, it would be nice if it was for something they actually did and not for what people say they did."

## The problem

What Higgs and company did, albeit unwittingly, was to dynamite a huge boulder that

was blocking progress on the standard model of particle physics.

The standard model is a quantum field theory, so it focuses on quantum waves or "fields"

that describe the probability of finding various particles here and there. It contains fields for the dozen types of matter particles—including electrons, the up quarks and down quarks that make up protons and neutrons, and the heavier analogs of those particles that emerge in high-energy particle collisions.

These particles interact through three forces: the electromagnetic force that binds the atom, the strong nuclear force that binds quarks into protons and neutrons, and the weak nuclear force, which produces a kind of radioactivity. (The standard model does



**Name recognition.** Peter Higgs was one of six theorists to have the same idea.

## Online

**sciencemag.org**

Podcast interview with writer Adrian Cho ([http://scim.ag/pod\\_6100](http://scim.ag/pod_6100)).

CREDIT (TOP TO BOTTOM): ATLAS; DENIS BALIBOUSE/REUTERS/LANDOV



**See?** Within the ATLAS particle detector, a particle collision appears to produce a Higgs boson that decays into two pairs of electrons (red and blue).

not include gravity.) The forces are conveyed by particles of their own, known collectively as “gauge bosons.”

The whole kit and caboodle is encoded mathematically in one master function called the Lagrangian, which describes everything physicists know about how particles and their force fields behave (see sidebar, p. 1288). Here’s the most important point in the whole theory: The standard model Lagrangian possesses three different mathematical symmetries called “local gauge symmetries,” which predict the existence of the three forces in the theory: weak, strong, and electromagnetic. For example, the simplest local gauge symmetry generates the quantum field for the photon, the gauge boson that conveys the electromagnetic force.

The connection between local gauge symmetries and forces is so strong that it defines the standard model, says Fermilab’s Quigg. “I don’t know that it’s a miracle, but it’s a wonderful thing,” he says. To construct the standard model, theorists had to find the Lagrangian with the right gauge symmetries to explain the observed forces.

In the early 1960s, however, physicists were just beginning to appreciate the importance of gauge symmetry. In 1961, Sheldon Glashow, now at Boston University, developed a model based on two gauge symmetries that described both the electromagnetic force and the weak force, which is carried

by particles now known as the W boson and the Z boson. There was a hitch, however: Because the weak force acts at extremely short range—far shorter than the width of an atomic nucleus—theorists knew the bosons that convey it must be massive, as the more massive a gauge boson is, the shorter its range. But simply tweaking the Lagrangian to give the W and Z particles mass spoiled the very gauge symmetry that predicted their existence.

To salvage gauge symmetry as the origin of forces, theorists needed to find a way to

system settles into its lowest energy state. For example, a marble in a round-bottomed bowl settles in the middle, the point of greatest symmetry. But if the center of the bowl has a hump like the “punt” in a wine bottle, the marble won’t stay in the middle but will run downhill in some random direction. The symmetry of the bowl remains in the setup, but the marble’s “choice” of direction makes it harder to see.

Spontaneous symmetry breaking had already been used to describe magnetism, superconductivity, and the formation of crystals. Years before the discovery of quarks, a pair of theorists had even developed a rough theory of the interactions of protons and neutrons through the strong force. Particle theorists hoped the concept would illuminate other issues, too.

But there was a snag, as Jeffrey Goldstone, now at the Massachusetts Institute of Technology in Cambridge, pointed out in 1961. He considered the simplest example, a quantum field that interacts with itself to produce an energy landscape or “potential” much like the wine-bottle bottom (see sidebar, p. 1289). In that case, the field can minimize its energy not in the usual way by vanishing but rather by taking on a nonzero strength in the vacuum. Some theorists speculated that the vacuum might not be as bland as they had assumed and might contain a hidden quantum field instead.

Unfortunately, Goldstone proved, any such field should produce massless particles known generally as Goldstone bosons. Such massless particles aren’t seen flitting about. So Goldstone’s theorem suggested that spon-



**The rest of the gang.** The other theorists who, in independent teams, figured out the “Higgs mechanism” include (from left) Tom Kibble, Gerald Guralnik, Carl Hagen, Francois Englert, and Robert Brout. Brout died in 2011.

give force-carrying particles mass without wrecking the symmetry.

### The solution

That’s exactly what Higgs and five others did, although they weren’t particularly thinking about the W and Z bosons. Instead, they were toying with a concept called “spontaneous symmetry breaking,” a process that occurs whenever the inner workings of a system possess a symmetry that gets lost as the

## Why the ‘Higgs’?

The physics behind the Higgs boson was first reported in August 1964 by Francois Englert and the late Robert Brout of the Free University of Brussels. Yet the particle bears the name of Peter Higgs of the University of Edinburgh in the United Kingdom. Why? Mistaken citations could be at fault, Frank Close of the University of Oxford in the United Kingdom wrote in his book *The Infinity Puzzle*.

Benjamin Lee, a Korean-American theorist who died in 1977, apparently used the term “Higgs boson” as early as 1966. But what made the term stick may have been a seminal paper Steven Weinberg, now at the University of Texas, Austin, published in 1967. In it, Weinberg cited a paper of Higgs’s from *Physics Letters*, volume 12, and his key paper from *Physical Review Letters*, volume 13, before the paper by Englert and Brout from

*Physical Review Letters*, volume 13. In fact, Higgs’s first paper appeared 2 weeks after Englert and Brout’s paper, and his key paper 5 weeks later still. Weinberg cemented the error in 1971 by mistakenly citing Higgs’s earlier paper as being in volume 12 of *Physical Review Letters*, making it appear that he had clearly been first. That error propagated through the literature for decades, appearing in the 2010 version of the *Review of Particle Physics*, the standard reference in the field. Weinberg acknowledged the mix-up in an essay in *The New York Review of Books* in May 2012. —A.C.



Steven Weinberg



taneous symmetry breaking just doesn't apply to real-world particle physics.

Then Higgs and two groups of other theorists independently found a way out of this particular jam. "The Goldstone theorem was a definite setback, so it was natural that people would try to find a way around it," says Tom Kibble of Imperial College London. Goldstone, the theorists realized, had considered a quantum field that interacts only with itself, and he didn't include local gauge symmetry or force-carrying gauge bosons. So they mixed those things into Goldstone's model, with two striking results. The pesky Goldstone bosons disappeared, and the force-carrying particles became massive.

Why does this happen? Physically, the force-carrying particles interacted with the new "Higgs field" produced by the spontaneous symmetry breaking to acquire energy and mass, in keeping with Albert Einstein's dictum that energy equals mass. Crucially, that happens without ruining the gauge symmetry, which is built into the theory from the start. The Higgs boson is a byproduct of the process. The Higgs field itself must consist of massive quantum particles lurking "virtually" in the vacuum, and those particles are Higgs bosons.

The theorists reported their solution in a string of papers in *Physical Review Letters* in 1964. Free University of Brussels research-

ers Francois Englert and Robert Brout, who died in 2011, reported their work on 31 August 1964. Higgs published 7 weeks later. Gerald Guralnik, now at Brown University; Carl Hagen, now at the University of Rochester in New York; and Kibble followed suit on 16 November. The papers made scarcely a ripple in the pond of theoretical physics. "Nobody took any notice of it at all," says Oxford's Close. The authors suggested that their mechanism might help explain strong interactions, but they didn't follow up on that possibility.

In fact, this "Higgs mechanism" was just the thing theorists needed to give mass to the W and the Z bosons that carry the weak force. That didn't occur to its inventors, however. "One of the puzzles is why somebody didn't get the idea to put these two ideas together immediately in 1964," Kibble says. "All the material was there." Instead, the seminal application was made in 1967 by Steven Weinberg, a theorist now at the University of Texas, Austin, and independently in 1968 by Abdus Salam, a Pakistani theorist who died in 1996 (see sidebar, p. 1287). "We gave them the tool they had to have," Guralnik says. Glashow, Weinberg, and Salam would share the Nobel Prize in 1979 for discovering the theory of the "electroweak force" and giving birth to the standard model.

### Big deal?

Given that complicated history, some theorists question whether the advance made by Higgs and his cohort really merits science's highest honor. They cite several possible arguments against it.

*The Higgs mechanism didn't push far enough past earlier work.* Several other physicists applied spontaneous symmetry breaking to particle theory before Higgs and company did, and some got close to the idea of the Higgs mechanism, says Michael Peskin, a theorist at SLAC National Accelerator Laboratory in Menlo Park, California. Goldstone was one such pioneer; another was Yoichiro Nambu of the University of Chicago in Illinois, who shared the Nobel Prize in 2008. Peskin acknowledges that the mechanism was controversial when first published in 1964. Even so, he says, "as someone who was educated in particle physics after 1972, it's hard for me to figure out what Higgs *et al.* did that was nontrivial."

In fact, Philip Anderson, a condensed matter theorist now at Princeton University, sketched out the basic idea very roughly in 1963. Goldstone says he came up with the same scheme in 1962, but senior colleagues convinced him that he was on the wrong

## Symmetries and Forces

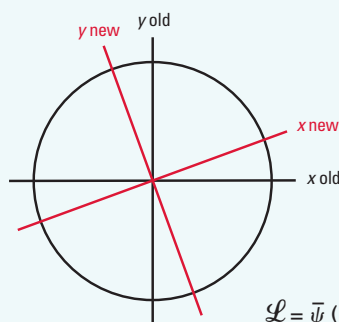
Particle theory is a model of efficiency. The standard model focuses on quantum fields that describe the distribution of the various particles in the model, and physicists roll all those fields into a single mathematical function called the Lagrangian that encodes all possible particle interactions. The Lagrangian possesses certain mathematical symmetries called local gauge symmetries that determine the exact nature of the forces between particles. That is, you can mix up the quantum fields in the Lagrangian in certain ways that leave the function looking exactly the same, and those symmetries predict the number and nature of the forces in the model.

The connection between symmetries and forces stems from a theorem published by the German mathematician Emmy Noether in 1918. She proved that if the Lagrangian describing a physical system—be it a molecule or a solar system—possesses a symmetry, then some overall aspect of the system must remain constant, or be "conserved." For example, if the Lagrangian is symmetrical with regard to posi-

tion—meaning you can take the whole system and move it in any direction without changing its behavior—then momentum must be conserved. If the Lagrangian is symmetrical with regard to time—meaning that you can slide the whole works forward or backward in time without affecting its behavior—then energy is conserved.

Gauge symmetries are more complicated, but they, too, lead to conservation laws. In this case the conserved quantities are charges like the electric charge. The standard model possesses three distinct gauge symmetries, which define the charges for the electromagnetic, weak, and strong forces. The characteristics of the charges then determine the characteristics of the forces and the quantum particles that convey them. For example, there is one type of electric charge, and the electromagnetic force is carried by uncharged photons. The strong force has three types of charges—red, blue, and green—and is conveyed by particles called gluons, which themselves are colored with those charges.

—A.C.



**Symmetry made simple.** The equation for a circle,  $x^2 + y^2 = 1$ , remains the same no matter how you rotate the axes on which the circle is drawn, even though the rotation mixes up the original  $x$  and  $y$  variables. In the same way, the standard model Lagrangian remains the same under more complex changes of variables called local gauge transformations. For example, the Lagrangian for just electrons (described by the quantum field  $\psi$ ) and photons (describe by the quantum field  $A$ ) doesn't change if  $\psi$  and  $A$  are redefined as shown below, where  $f(x)$  is any function of space and time and  $\partial$  is the derivative sign.

$$\mathcal{L} = \bar{\psi} (i\gamma^\mu \partial_\mu - m)\psi - \frac{1}{4}(\partial_\mu A_\nu - \partial_\nu A_\mu) \cdot (\partial^\mu A^\nu - \partial^\nu A^\mu) - e\bar{\psi}\gamma^\mu A_\mu\psi$$

$$\psi \rightarrow e^{if(x)} \cdot \psi$$

$$A^\mu \rightarrow A^\mu + \partial^\mu f(x)$$

## Spontaneous Symmetry Breaking Decanted

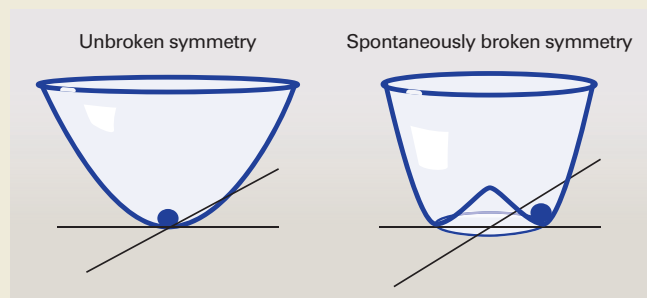
Ordinarily, a quantum field reaches its lowest energy when it vanishes (see figure, left). But the field can interact with itself to produce an energy landscape resembling a wine-bottle bottom, with a hump in the middle and a circular trough surrounding it. The field can then minimize its energy by rolling downhill, just as a marble placed in the wine bottle would (see figure, right). To do so, the field must take on a nonzero strength and randomly choose a direction in an abstract two-dimensional “phase space,” breaking the symmetry of the situation.

When such spontaneous symmetry breaking occurs, different kinds of particles emerge, as can be seen by pushing the marble analogy further. Suppose the marble jiggles; such jiggling corresponds to the existence of particles in the quantum field theory. Jiggling along the trough costs no energy and corresponds to massless particles, known as Goldstone bosons. Jiggling across the trough and uphill in the energy landscape costs energy and corresponds to the existence of massive particles.

In the so-called Higgs mechanism, the massless Goldstone bosons

meld with other massless force-carrying particles to make the force-carrying particles massive. The weighty particle corresponding to the uphill jiggling remains. It is the Higgs boson.

—A.C.



**Energy landscapes.** The horizontal distance from the origin corresponds to a quantum field's strength; the height corresponds to the field's energy.

track. “So I lost my nerve,” he says. “The only evidence for this story is that I’ve told it many times over the years. I don’t even have a scrap of paper. And it only proves that I wasn’t thinking clearly.” If at least eight people have the same idea, how brilliant can it be? “That’s a fair question,” acknowledges Close, who supports a Nobel for the work.

*Higgs and company did not predict the standard model Higgs boson in the sense that physicists understand it today.* It’s true that a massive new particle is a byproduct of the physics described in the 1964 papers. And the observation of that particle is vital, as it confirms that nature really is using the Higgs mechanism, says Gordon Kane, a theorist at the University of Michigan, Ann Arbor: “Otherwise, the whole theory is bullshit.”

But the *specific* particle that researchers at CERN apparently discovered this summer, with all its predicted properties, emerged only later, during the construction of the actual standard model. “The Higgs field of the weak interactions—the real Higgs field, in other words—was the idea of Weinberg and Salam,” Peskin says.

*Higgs didn’t explain the origin of mass.* Despite breathless headlines to the contrary, even the standard model Higgs mechanism does not explain the existence of all mass in the universe. The Higgs mechanism does give mass to the W and Z bosons. And Weinberg showed how it could give mass to other *fundamental* particles such as electrons and quarks. But most of the visible mass in the universe resides in protons and neutrons, which are not fundamental particles. And most of their mass comes from the binding energy among their component quarks.

### Favorites and long shots

Caveats aside, many physicists say that the advance Higgs and colleagues made—finding a way to give mass to force-carrying particles without screwing up the whole theory—definitely merits a Nobel Prize. The Higgs mechanism implies that the empty space is threaded by a new type of quantum field, Kane says, so its confirmation at CERN revolutionizes physicists’ understanding of the universe. “I would say it’s the most exciting thing in particle physics ever—no qualification,” he says.

If the Nobel committee agrees, its members will decide who should get the prize. That’s a tricky question, as at most three people, still living, can share the Nobel. At first blush the answer might seem obvious: Englert and Brout published first; Higgs, second; and Guralnik, Hagen, and Kibble, third. And in science, the race goes to the swiftest.

But the contents of the papers, none more than three pages long, make matters less clear. Englert and Brout present only an approximate “first order” calculation. Higgs presents only a classical field theory argument and states in a footnote that “nothing is proved about the quantized theory.” Guralnik, Hagen, and Kibble present an analysis that other physicists say is more complete.

Some say the issue comes down to who predicted the existence of the Higgs boson itself. “Higgs has an unassailable case because he is the guy who realized there would be a massive boson,” says John Ellis, a theorist at King’s College London.

However, in his 1964 paper, Higgs’s discussion of the new particle consists of just one sentence—“Equation (2b) describes waves whose quanta have (bare) mass  $2\phi_0\{V''(\phi_0)\}^{1/2}$ ”—and it clearly wasn’t the focus of his work. And the fact that a quantum field consists of quantum particles goes without saying, physicists point out, so it hardly counts as a mark against the other theorists if they didn’t mention it explicitly.

Asked to prophesy, Ellis, Close, and Kane all say that Higgs is a shoo-in for the Nobel and that Englert has a strong case for priority. Guralnik, Hagen, and Kibble are likely to get left out. “They were scooped, and that’s a fact of life,” Close says—although he and the others agree that Kibble might get the nod for applying the mechanism to more complex gauge sym-

metries and paving the way for Weinberg and Salam.

Some theorists say a Nobel Prize should go to the experimenters who discovered the new particle. That may seem ludicrous, as the two teams that spotted it comprise 3000 members each. But “choosing one out of [each] 3000 might be easier than choosing three out of six,” Quigg says. Peskin says Lyndon Evans, the accelerator physicist at CERN who led the construction of LHC, clearly deserves the prize.

Nominations for this year’s prizes closed in February, so a Nobel for the discovery of the Higgs probably won’t come until 2013 at the earliest. That leaves plenty of time to place your bets.

—ADRIAN CHO

*“If these people receive their rewards, either in heaven or before, it would be nice if it was for something they actually did.”*

—CHRIS QUIGG,  
FERMILAB





## BIOACOUSTICS

# The Sound in the Silence: Discovering a Fish's Soundscape

**Bioacoustics pioneer Arthur Popper is getting ready to retire, but his work on how fish perceive sound isn't fading away**

As an undergraduate more than 40 years ago, Arthur Popper took a detour on his way to a class on New York University's campus in the Bronx that set him on a course to become the godfather of fish hearing. Popper decided to visit a new pet shop, where he spied a fish without eyes. He began thinking about how it lived guided by its other senses. The encounter eventually led Popper, now a bioacoustician at the University of Maryland, College Park, to become one of the world's pioneers in understanding how fish perceive and respond to sound. "If I hadn't walked by that shop that day," he says, "I'd have a different life."

Today, Popper's professional life is defined by sound. Among bioacoustics researchers, he's widely known for the classic drawings of fish ear anatomy he produced as a young scientist and for co-editing a series of influential books that colleagues say has helped shape the growing field. Popper has also conducted innovative studies that have documented the effects of human-generated sound on fish and raised questions about the science underpinning government regulations designed to protect sea life from industrial noise. "I knew he was going to be successful as a scientist," says sensory biologist William Tavolga of the Mote Marine Laboratory in Sarasota, Florida, who over-

saw Popper's doctoral work. "But there was no predicting the huge amount of work he's done and the quality of work."

And now that the irrepressible 69-year-old researcher is preparing for retirement, colleagues are wondering if anyone can take Popper's place—and whether he'll actually slow down. "I'm amazed at the energy of the guy," says marine biologist Robert Gisiner of the U.S. Navy's Energy and Environmental Readiness Division in Washington, D.C. "He could just run me into the ground and I'm 10 years younger."

### An unanswered question

When Popper was growing up in New York City in the 1950s, many people still shared the notion of a silent ocean, popularized by the explorer Jacques Cousteau. That view has profoundly changed. We now know that many marine animals use sound to find food, avoid predators, and communicate. And humans have added their own cacophony: the thrum of ship screws, the blast of seismic air guns for oil exploration, and the concussive force of pile drivers used to build docks and bridges. Popper was one of the first to make the scientific community aware that humanmade noise could affect the behavior and health of animals other than marine mammals, says neuroethologist Darlene Ketten, who holds a joint

**The godfather.** Bioacoustician Arthur Popper (with the HICI-FT) used to test the effects of sounds produced by pile drivers on fish.

appointment with the Woods Hole Oceanographic Institution and Harvard Medical School, both in Massachusetts.

As a graduate student at the City University of New York in the late 1960s, Popper initially wanted to focus on how blind fish determined where sound came from. "[It's] called sound-source localization," and the ability is considered to be one of the most powerful forces driving the evolution of hearing, Popper says. "Because if you just hear a sound and don't know where it's coming from, it's not worth hearing."

But sound bounced around in the fish tanks available to Popper at the time, making experiments impossible and forcing him to abandon his localization project. Even today, the question is hard to study, he says. "We know [fish] can localize sound, but how well and how they do it is still a mystery." Instead, Popper moved on to studying the hearing capabilities of Mexican blind cavefish (*Astyanax jordani*) and its eyed ancestor (*Astyanax mexicanus*). He discovered that these species had the widest hearing range yet measured in fish, and that blind cavefish didn't necessarily sense pressure stimuli better than their eyed relatives. After earning his doctorate, Popper ultimately landed jobs at the University of Hawaii, Manoa, and then at the Georgetown University School of Medicine in Washington, D.C., where he taught neuroanatomy.

In 1975, Popper learned scanning electron microscopy during a sabbatical, opening a new window into fish hearing. He used the skill to delve into the form and function of a fish's inner ear, mapping the orientation of hair cells and showing that fish can actually regenerate damaged ones.

"One of Art's biggest contributions was the anatomy he did on fish hearing," says longtime collaborator Anthony Hawkins, a bioacoustician and former head of fisheries research for Scotland. Researchers still use some of Popper's elegant, detailed drawings, he says: "We still don't know how it all works. But we have a lot of information on their anatomy."

Then, in the early 1990s, Popper began co-editing a series of books—called the Springer Handbook of Auditory Research (SHAR)—with his longtime friend and collaborator, fish-hearing specialist Richard Fay. There are now 45 volumes, and each is meant to aid investigators in understanding an area of hearing research they aren't necessarily experts in. Popper and Fay enlist

specialists to cover topics as diverse as hearing in bats and music perception. “Hearing research has been changed by [the SHAR] series,” Ketten says.

### A hissy fit

In the last few decades, Popper has become known for figuring out how to conduct difficult experiments that examine how fish respond to sound both in the field and in the laboratory. One focus is understanding how the noise produced by pile drivers—widely used machines that pound supports for bridges and docks into bottom sediments—affect fish and other aquatic creatures that are protected by environmental regulations.

“When people do experiments with very loud sounds, [they] usually have to do it in the field because you can’t simulate loud sounds in the laboratory,” Popper says. That’s because the volume is just too intense: For pile drivers, the sound can be louder than turning on a jet engine in a room.

But field experiments aren’t easy. Piggybacking on construction projects while the crew tries to stay on schedule, for example, is less than ideal. And workers are not going to stop and wait while you get your fish into place, Popper says. As a result, past field trials had been “very weakly done, poorly controlled, by people who really don’t understand how to evaluate the results of these experiments,” he laments.

In 2004, he decided to see if he could bring the studies into a controlled lab setting after a frustrating consulting experience trying to determine safe noise thresholds for fish during pile-driving operations on the San Francisco–Oakland Bay Bridge in California. The trick was finding a device that produced the needed racket without deafening researchers.

The solution came from a colleague, mechanical engineer Peter Rogers of the Georgia Institute of Technology in Atlanta. As part of a Navy study of the possible health effects of loud underwater noise on divers, Rogers had built a machine that allowed scientists to study how high-intensity sounds affected the lungs of submerged rats outfitted with a kind of rodent scuba gear. Rogers modified the machine for use with fish, producing what Popper affectionately refers to as the “hissy fit,” short for high intensity controlled impedance fluid-filled wave tube (HICI-FT).

It took about 2 years for Popper’s lab to

work out the kinks, but the machine now presides over a small room at the University of Maryland. A red metal frame supports a steel cylinder with 8.9-centimeter-thick walls, centered between two large shakers that vibrate, generating pressure waves akin to those produced by a pile driver. Tubes surrounding the HICI-FT draw away the enormous amount of heat generated by the shakers, and it perches on vibration isolation mounts to prevent it from shaking the entire building. Fish placed inside the chamber are exposed to sound levels they would experience if they were swimming up to 18 meters away from a pile-driving operation.

Several years ago, Popper and colleagues at the University of Maryland and the Pacific Northwest National Laboratory in Richland, Washington, started by giving juvenile Chi-



**Hearing capabilities.** Fish hearing specialist Arthur Popper is not afraid to get dirty while trying to elucidate hearing sensitivity in walleye pollock.

nook salmon (*Oncorhynchus tshawytscha*) a hissy fit; regulators were interested in the experiments because the fish is an endangered species. They’ve since repeated the process with other species, including striped bass (*Morone saxatilis*) and lake sturgeon (*Acipenser fulvescens*).

The HICI-FT results, parts of which were published online June 2012 in *PLoS ONE*, show that the physiological effects experienced by the fish depend on the sound intensity and accumulated exposure. At lower sound levels, the pressure shifts caused by pile driving might cause minor blood vessels in fins to break and leak. Fish exposed to higher intensity sounds, however, could experience lethal and deafening injuries such as hemorrhaging of the heart and deflated or

ruptured swim bladders. In some species, swim bladders both help fish regulate their buoyancy and conduct sound into the ear. Damaging the swim bladder could essentially renders species such as catfish hard of hearing. Popper and his colleagues also found that the sound thresholds needed to induce such trauma were higher than what people had previously thought. The take-home message, he says, is that the sound levels that regulatory agencies have been using as safety limits for fish are lower than necessary.

### A working retirement

Although Popper would love to test other anthropogenic sounds fish encounter using the HICI-FT, it is headed back to the Transportation Research Board of the U.S. National Academies, which funded the device. It’s just one loose end he’s tying up as he prepares to retire in June 2013.

But even after taking his leave, Popper will have projects bubbling. This past June, for instance, he flew out to California to check on work he’s started with tuna researcher Barbara Block of Stanford University in Palo Alto. Popper is helping train bluefin tuna (*Thunnus thynnus*) to respond to different sound levels in a bid to elucidate what the marine predators can hear. “It’s the old operant-conditioning paradigm where the animal works for a food reward,” he explains. The sleek animals have taken to the task, Popper hints, although he is cagey about the details since it’s a work in progress. He’s also helping plan a third international conference on the effects of noise on aquatic life, set for Budapest in August 2013. (He helped kick off the meetings in 2007.)

First, however, many of Popper’s students and colleagues will gather in Florida next year to honor the researcher some call the “godfather” of their field. “Art is an amazing person all around and an excellent role model for anyone in science,” Ketten says. Former students say that although Popper expected members of his lab to work hard, he also knew how to have fun, teasing lab members and colleagues. A few turn the tables: “Every now and then I threaten to take his Ph.D. away from him,” says Tavalga, who was Popper’s dissertation adviser. “But he says I can’t do that because there’s a statute of limitations.”

—JANE J. LEE

Jane J. Lee is a writer in Washington, D.C.





## LETTERS

edited by Jennifer Sills

## Paying for Tissue: The Case of WI-38

IN THEIR POLICY FORUM "PAYING PATIENTS FOR THEIR TISSUE: THE LEGACY OF HENRIETTA LACKS" (6 July, p. 37), R. D. Truog *et al.* overlook the L929 cell line, which, contrary to their statement about HeLa, was the first immortal cell line (1). Also overlooked are the commercial uses and questions of legal ownership first raised for normal human cell strains (2). WI-38, derived from the lung tissue of a surgically aborted fetus, has not only been used in research worldwide whenever a normal human cell is required, but has also been used as the substrate for the production of many of the world's human virus vaccines since the mid-1960s. About 2 billion people have directly benefitted from the use of WI-38 and similar strains (3). Although the commercial sales of vaccines produced in WI-38 cannot be accurately determined, it is certainly in the multiple billions of dollars. In the 1960s, I distributed WI-38 gratis to vaccine manufacturers and researchers worldwide because biological material could not be patented.



Truog *et al.* seem unaware that in 1975, the National Institutes of Health (NIH), Food and Drug Administration (FDA), and Department of Health, Education, & Welfare (DHEW) argued that the WI-38 I used in my research was the sole

property of the U.S. government. I and my colleagues had never received government support for the research or development of WI-38. In response to the government's claims of propriety, we sued. We believed that there are several stakeholders in the title to any human cell culture: the researchers who actually developed the culture, their institution, the individual from whom the tissue was derived, and the organization that supported the research.

During the 7 years of litigation, several decisive events torpedoed the government's position that it had sole title to WI-38. First, the Supreme Court decided that biological material could be patented (4). This decision established the principle that, even with federal research support, biological researchers have patentable intellectual property rights for their discoveries.

Second, the Bayh-Dole Act reversed the presumption of government title. Bayh-Dole permits a university, small business, or nonprofit institution to claim as its intellectual property the control of an invention in preference to the government and despite federal funding (5). The act further provides that royalties be shared with the inventor.

Third, in 1983, President Reagan instructed federal agency heads that all businesses should be able to retain patent rights on inventions made in the course of government-funded R&D work. His executive order explained that giving the private sector clear title to patents on inventions developed under federal contracts and grants would lead to more rapid commercialization of new products (6).

Fourth, the nascent biotechnology industry was then being formed by entrepreneurial biologists whose companies were founded by using biological materials discovered in federally funded university research laboratories. Thus, the NIH found itself in the untenable position of first claiming sole title to WI-38 by alleging that it was discovered using federal funds and later praising the use of federal funds to discover biological materials that were then used in the founding of new biotechnology companies.

The Justice Department, which defended the NIH, FDA, and DHEW, recognized their con-

tradictory positions and accepted an out-of-court settlement. This is the first, and perhaps the only, instance where an individual scientist obtained federal legal title to a normal human cell strain, an event contradicted by subsequent state court decisions. The question of title to a self-duplicating human cell line or strain is still, after 50 years, a controversial issue.

LEONARD HAYFLICK

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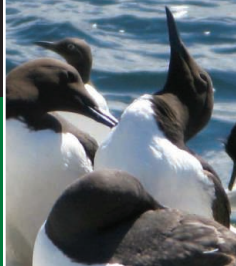
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## Paying for Tissue: Net Benefits

IN THEIR POLICY FORUM "PAYING PATIENTS for their tissue: The legacy of Henrietta Lacks" (6 July, p. 37), R. D. Truog *et al.* oppose sharing biomedical research revenues with the patients whose tissues enable that research. They argue that "reconceptualizing tissue acquisition as an economic exchange rather than as a gift relationship" might reduce tissue donation by "crowd[ing] out" altruistic motivations. We are skeptical of this argument.

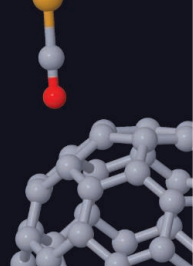
The possibility of compensation might crowd out some individual donations, but other altruism-motivated donations would increase because of compensation, and non-altruistic donations would also increase. It thus seems unlikely that net willingness to supply tissue would decline. Patients for whom compensation would truly decrease the enjoyment of donating tissues could pass on their compensation to nonprofits such as the American Cancer Society.

Truog *et al.* also argue that offering com-



Routes to  
cooperation

1304



Probing  
chemical bonds

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pensation proportional to tissue value would be “unjust” because patients whose tissues yield “financial blockbusters” would be paid more than the vast majority of donors. This argument, too, is unconvincing. “Blockbuster” cell lines make some researchers very rich, whereas other researchers do not benefit at all; is that unjust? Moreover, it is standard to tie compensation to the value of personal characteristics such as intelligence or athletic ability. How could such a system, if applied to compensation for tissue donation, be less fair to patients than the current system, under which all revenues from tissue lines—“blockbuster” or otherwise—accrue to the medical community?

Offering value-based compensation to tissue donors would likely boost tissue supply. The great majority of patients would likely be willing to donate waste tissue in exchange for either a fixed fee or a chance to share in the rewards of financially successful research.

SCOTT D. KOMINERS<sup>1\*</sup> AND GARY S. BECKER<sup>2</sup>

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## Response

KOMINERS AND BECKER ARGUE THAT COMPENSATING patients for their tissue will increase the supply of tissue for research. But there is no evidence that lack of compensation, the current standard, is an impediment to procurement of tissue. This is tissue that will be discarded if it is not used for research, and we doubt that very many patients refuse to give permission for the use of such tissue or that those who do refuse would reconsider if offered compensation.

Kominers and Becker propose compensation mechanisms that would be complex and difficult to implement. Compensation to the patient could not be linked to the actual value of the tissue at the time of donation, because it is impossible to know the value of waste tissue at that point. It could be many years before it is known whether a sample has value. An alternative reimbursement scheme

based on a future royalty interest would lead to substantial transaction costs and would favor patients whose identity, location, and relatives could be easily tracked over time, thereby unfairly disadvantaging those with less social stability and family integrity.

Even the suggestion to consider a compensation scheme based on a fixed fee for all samples is problematic. If we are correct that the number of tissue samples that have little or no value dwarfs the number of those that do (an empirically testable question), the actual amount of the fixed fee would likely be quite small. While it is difficult to predict the effect that a small amount of compensation would have on the willingness of patients to donate, some empirical evidence does suggest that small payments can decrease altruistic behavior in comparison with no payments at all (*1*). The complexity and costs to the research enterprise of any of these mechanisms would need to be justified by a positive argument about why those who donate waste tissue deserve financial compensation, an argument that Kominers and Becker do not provide.

Finally, on the question of fairness, we disagree with the authors that there is anything unfair about rewarding medical researchers for their ingenuity, talents, hard work, and willingness to take risks and to absorb opportunity costs in transforming medical waste into products that have scientific value.

We want to be clear that our Policy Forum only analyzed whether donors of waste tissue should receive financial compensation. Other forms of compensation, such as recognition or commitments to use a portion of the proceeds for other worthwhile purposes, are commendable and entirely appropriate. Indeed, when the research is federally funded, all proceeds retained by the academic institution, net of expenses such as the costs of protecting intellectual property, must be used for research and educational purposes, both important public goods. The question we addressed, however, focused only on the propriety of payments to the individual and family for the use of the original discarded specimen.

ROBERT D. TRUOG,<sup>1\*</sup> AARON S. KESSELHEIM,<sup>2</sup>  
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## Readers’ Poll

### Paying for Tissue

The family of Henrietta Lacks never received any financial compensation for the HeLa cell line, which was derived from the tissue that researchers obtained during her treatment for cervical cancer. Her story has raised the question of whether patients should be compensated for such tissue. In their Policy Forum (6 July, p. 37), R. D. Truog *et al.* argue against payment. They explain that the tissue only becomes valuable once research has been done by investigators. Once the prospect of money has been introduced, insufficient payments might provide a disincentive for donation. Payments would open the door to researcher biases affecting distribution, and patients would inevitably be compensated unequally, given that some cell lines lead to far more revenue than others. In their Letter (this issue, p. 1292), Kominers and Becker disagree with Truog *et al.* They argue that financially compensating patients would likely lead to a net increase in donations. They then suggest that unequal distribution of revenue does not make the system unethical; investigators currently reap unequal rewards for their work with the tissues in question. Truog *et al.*’s Letter Response (this issue, p. 1293) highlights the logistical challenges of implementing a fair payment system. What do you think?

**When medical procedures result in tissue that would otherwise be discarded, should researchers be required to pay patients for its use?**

- ☐ Yes  
☐ No

Vote online at <http://scim.ag/tissuepoll>

Polling results reflect the votes of those who choose to participate; they do not represent a random sample of the population.



## CORRECTIONS AND CLARIFICATIONS

**Editorial:** "Iceberg alert for NIH" by H. R. Bourne and M. O. Lively (27 July, p. 390). The Editorial mistakenly indicated that 150 research faculty were laid off by the University of Miami's Miller School of Medicine. This sentence should have said that "researchers" were laid off (not "110 researchers" as indicated in the original correction). The text has been corrected in both the HTML and PDF versions online.

**News & Analysis:** "Stability at last for Australian Synchrotron?" by E. Finkel (20 July, p. 278). In the third paragraph, the story incorrectly stated that "seven of nine members of the synchrotron's International Scientific Advisory Committee resigned." In fact, five of nine members resigned.

## TECHNICAL COMMENT ABSTRACTS

### Comment on "Climate Sensitivity Estimated from Temperature Reconstructions of the Last Glacial Maximum"

J. Fyke and M. Eby

Schmittner *et al.* (Reports, 9 December 2011, p. 1385) report a new, low estimate of equilibrium climate sensitivity based on a comparison of Last Glacial Maximum climate model simulations and paleoproxy data. Here, we show that exclusion of questionable comparison points and constructive changes to model design are both likely capable of altering the most probable value of equilibrium climate sensitivity suggested in Schmittner *et al.*

Full text at [www.sciencemag.org/cgi/content/full/337/6100/1294-b](http://www.sciencemag.org/cgi/content/full/337/6100/1294-b)

### Response to Comment on "Climate Sensitivity Estimated from Temperature Reconstructions of the Last Glacial Maximum"

Andreas Schmittner, Nathan M. Urban, Jeremy D. Shakun, Natalie M. Mahowald, Peter U. Clark, Patrick J. Bartlein, Alan C. Mix, Antoni Rosell-Melé

The removal of data by Fyke and Eby is mostly unjustified, and their statistics are oversimplified, but the suggestion that structural model uncertainty—in particular, the atmospheric heat flux formulation—may have led to underestimation of equilibrium climate sensitivity for a doubling of atmospheric carbon dioxide concentrations in our 2011 paper may have merit and should be quantified in future studies.

Full text at [www.sciencemag.org/cgi/content/full/337/6100/1294-c](http://www.sciencemag.org/cgi/content/full/337/6100/1294-c)

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# Comment on “Climate Sensitivity Estimated from Temperature Reconstructions of the Last Glacial Maximum”

J. Fyke<sup>1\*</sup> and M. Eby<sup>2</sup>

Schmittner *et al.* (Reports, 9 December 2011, p. 1385) report a new, low estimate of equilibrium climate sensitivity based on a comparison of Last Glacial Maximum climate model simulations and paleoproxy data. Here, we show that exclusion of questionable comparison points and constructive changes to model design are both likely capable of altering the most probable value of equilibrium climate sensitivity suggested in Schmittner *et al.*

Schmittner *et al.* (1) estimate equilibrium climate sensitivity (ECS) by comparing University of Victoria Earth System Climate Model (UVic ESCM) simulations with a range of ECS values to a composite of paleoclimate proxy records of Last Glacial Maximum (LGM) climate, surface air temperature (SAT), and sea surface temperature (SST). The UVic ESCM is an Earth system model of intermediate complexity, and here we highlight some structural uncertainties that, in our opinion, were not accounted for sufficiently in (1). Using a simple sensitivity analysis, we show that these uncertainties are likely capable of notably influencing their most likely ECS value.

We first regridded the model output from (1) and related land and ocean proxy data onto a common, high-resolution grid (0.2° by 0.2°) to facilitate direct comparison without introducing interpolation artifacts. Low-resolution grid quantities are applied as a single value over the equivalent area on the high-resolution grid. Comparison of model and observation data on this common grid highlights coastal model/observation data mismatches due to land-mask inconsistencies; these points were removed from model/observation comparison.

Over the land component, we found that the analysis in (1) erroneously compared model SAT over ice sheets to bare land pollen data (2) for several proxy SAT grid points. We excluded these data points from further analysis. Several high-latitude 2° by 2° proxy SAT grid points in Alaska describe remarkably strong gradients and temperatures, including high-latitude LGM temperatures up to 13.4°C warmer than present. For our sensitivity analysis, we excluded these data points because the simple, diffusive, coarse resolution UVic ESCM atmosphere would not be capable of capturing the high-gradient climatic

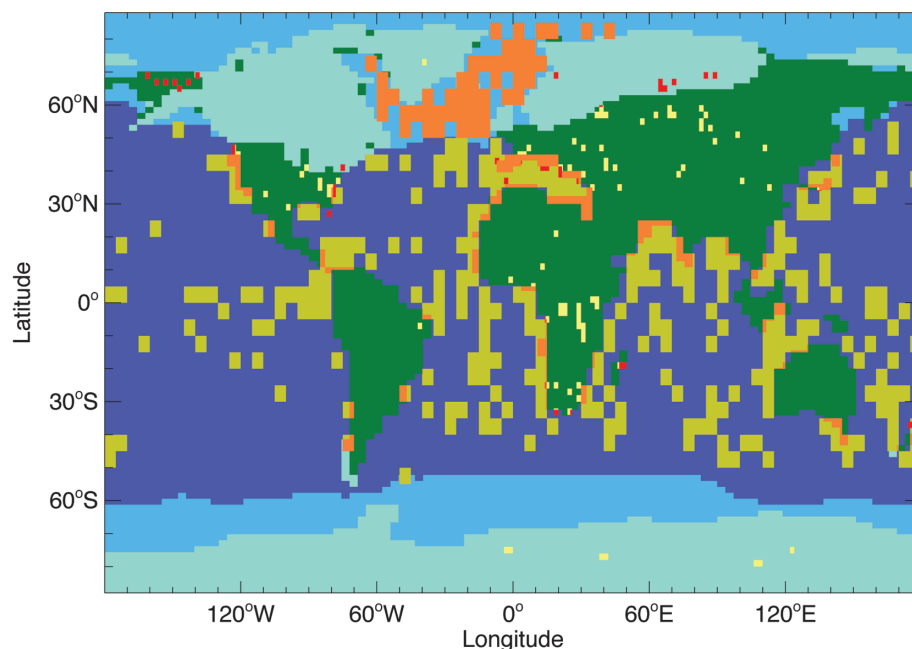
signal that the data suggests, introducing an error in any model-data comparison there.

The Multiproxy Approach for the Reconstruction of the Glacial Ocean Surface (MARGO) reconstruction suggests SSTs of up to 6.2°C warmer than present-day in the LGM high-latitude North Atlantic and Nordic Seas (3), with warm values due largely to dinoflagellate cyst data (4). Given discrepancies in North Atlantic paleo-SST data, members of the MARGO community note that “the average LGM SST in the Nordic Seas cannot at present be assessed with confidence” (4). More importantly, it is not clear that these warm MARGO-derived SST values can be directly compared with equivalent model output, given the presence of a strong North

Atlantic cold bias of up to −10°C (5) in this model. This cold bias is structural and strongly linked to anomalous sea-ice growth. In addition, we believe that the coarse vertical nature of the UVic ESCM ocean model makes any under-ice SST comparisons dubious. The presence of clear model weaknesses in this region overlaid on uncertain MARGO data led us to exclude oceanic data north of 50°N in the Atlantic, largely removing Arctic sea-ice-covered regions from model/observation comparisons.

The mask of included and excluded points is shown in Fig. 1. We note that excluding certain land and ocean data contributes to the very poor representation of the zonal mean at several latitudes.

Pointwise intermediate-complexity climate model (EMIC)–observation comparisons can generate residual error or “noise” related to the difference between overly smooth climate model output and observational data with strong spatial structure. For this reason, we believe that comparison of latitude-weighted zonal averages instead of analyses based on point-wise comparison is a more discriminating metric of large-spatial-scale EMIC performance, even when the zonal mean is not completely represented. Thus, to explore the first-order influence of comparison point removal on relative model ranking, we zonally averaged data-model differences and performed a relative ranking based on root mean square error (RMSE) of both the data-limited and original data sets (Fig. 2). We found that exclusion of questionable comparisons altered our version of the “best fit” model in (1). Although our statistical



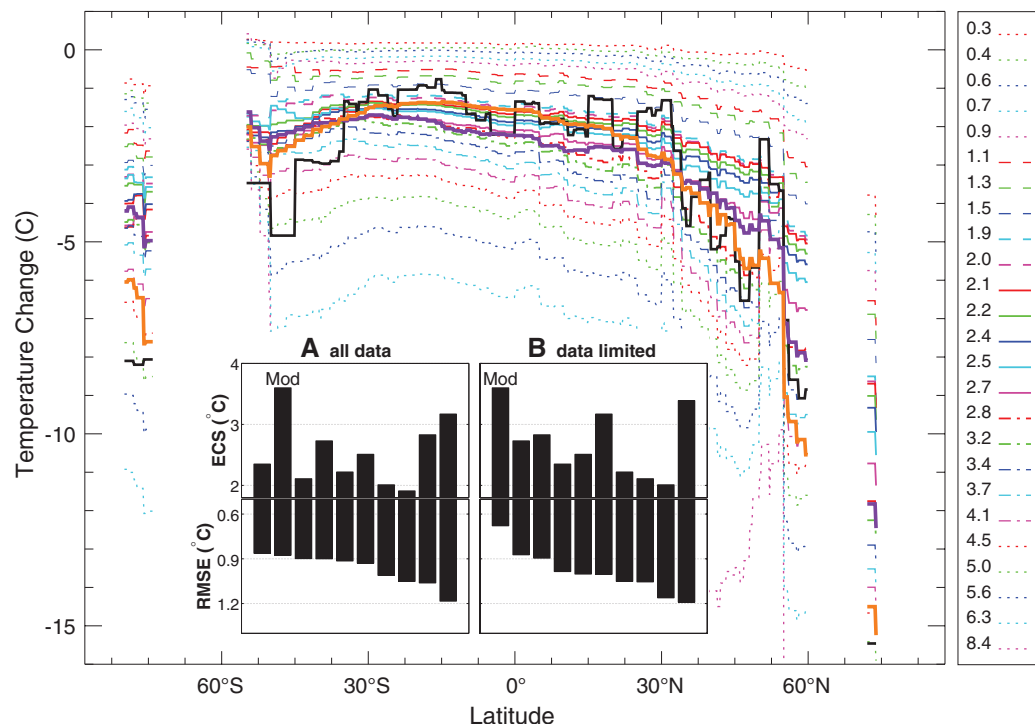
**Fig. 1.** Spatial map of included/excluded data. Yellow, included land data points; red, excluded land data points; olive, included MARGO data points; orange, excluded MARGO data points; turquoise, land ice; light blue, sea ice in medium-ECS simulation; dark green, model land; dark blue, model ocean. Removal of high northern latitude land and ocean points results in poor zonal coverage above 60°N.

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**Fig. 2.** Latitudinal average LGM-modern SAT/SST difference, with locations of questionable data-model comparisons removed. Black line, composite observations; thick orange line, simulation using a new version of the UVic ESCM with variable latitudinal atmospheric diffusion of heat (Mod); thick purple line, original default UVic ESCM LGM simulation; remaining thin lines, simulations from (1). **(Inset)** Latitude-weighted zonal average RMS-based comparison of top-ranking central model simulations from (1) and Mod, with (A) all data and (B) limited data. Top bars represent ECS; lower bars show RMSE for each simulation. (A) corresponds to the original analysis in (1), whereas (B) corresponds to the updated zonal average differences plotted here. The Mod simulation does notably better than the simulations in (1) at simultaneously matching both low-latitude observations and the few robust high-latitude observations when data are limited. With questionable model/data comparisons excluded, the high-ECS Mod simulation performs notably better than the nearest competitor in (1). The positions of the simulations in (1) also shift, with higher-ECS models moving up in ranking.



processing is simple compared with the analysis in (1), it suffices to demonstrate that model performance metrics are strongly dependent on the comparison points used in the analysis. While Schmittner *et al.* also note that removal of particular regions of the data affects their results, their final product results from point-wise comparison using all available locations, which we suggest is not optimal.

Finally, to explore the potentially large dependence of Schmittner *et al.*'s results on the choice of climate model, we carried out a new model simulation with the most recent version of the UVic ESCM in which the atmospheric latitudinal profile of heat diffusion varies in response to the global average atmospheric temperature anomaly (the "Mod" simulation in Fig. 2). This functionality gives a new model with much-improved fit to both Antarctic and Arctic LGM temperatures as recorded by ice cores, yet still retains an excellent fit to low-latitude tempera-

tures. Notably, and most importantly, we found that this model ranks very well with respect to the relative RMSE test, but with a much higher ECS (3.6°C) than similarly ranked models in (1). As suggested in (1), the lack of dust forcing in our LGM model may lower the equivalent ECS by ~0.3°C, but this is still well above the median ECS estimate of 2.3°C in (1).

In summary, we argue that structural model error limits the ability of the model to recreate some aspects of the LGM climate as reconstructed from available proxy data, and this results in nonphysical biases in any model/observation comparison. We also find that reasonable and constructive changes to model design change our best estimate of ECS dramatically. This implies to us that use of more robustly selected comparison points or a different model would likely change the results of (1); this puts into question the robustness of their main conclusions (namely, the low and well-constrained ECS value).

Thus, while the overall method is in principle an excellent way of constraining ECS, we suggest that inadequacies in the EMIC that limit it from capturing important aspects of the paleodata and the high dependence of "best-guess" ECS estimates on the choice of climate model preclude the conclusion by Schmittner *et al.* of a low and constrained ECS value.

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**Acknowledgments:** We thank Schmittner *et al.* for making all model output and paleodata (2, 3) freely available online.

2 March 2012; accepted 24 July 2012  
10.1126/science.1221371

# Response to Comment on “Climate Sensitivity Estimated from Temperature Reconstructions of the Last Glacial Maximum”

Andreas Schmittner,<sup>1\*</sup> Nathan M. Urban,<sup>2</sup> Jeremy D. Shakun,<sup>3</sup> Natalie M. Mahowald,<sup>4</sup> Peter U. Clark,<sup>5</sup> Patrick J. Bartlein,<sup>6</sup> Alan C. Mix,<sup>1</sup> Antoni Rosell-Melé<sup>7</sup>

The removal of data by Fyke and Eby is mostly unjustified, and their statistics are oversimplified, but the suggestion that structural model uncertainty—in particular, the atmospheric heat flux formulation—may have led to underestimation of equilibrium climate sensitivity for a doubling of atmospheric carbon dioxide concentrations in our 2011 paper may have merit and should be quantified in future studies.

Fyke and Eby (*1*) conclude that “exclusion of questionable comparison points and constructive changes to model design are both likely capable of altering the most probable value

of equilibrium climate sensitivity” to a doubling of CO<sub>2</sub> (ECS<sub>2xC</sub>) suggested in Schmittner *et al.* (*2*). Fyke and Eby modify the climate model used in (*2*) and remove data from the analysis. Together, this leads to a better fit [as indicated by the root mean square error (RMSE) of the zonally averaged difference between model and reconstructions] of their higher sensitivity (ECS<sub>2xC</sub> = 3.6 K) model than that of the best fitting model of (*2*), which had a lower sensitivity (ECS<sub>2xC</sub> = 2.4 K). Although the authors present tantalizing results, their conclusion is not fully substantiated by evidence, and we note that because they do not present probabilities, statements on the most probable value are inappropriate.

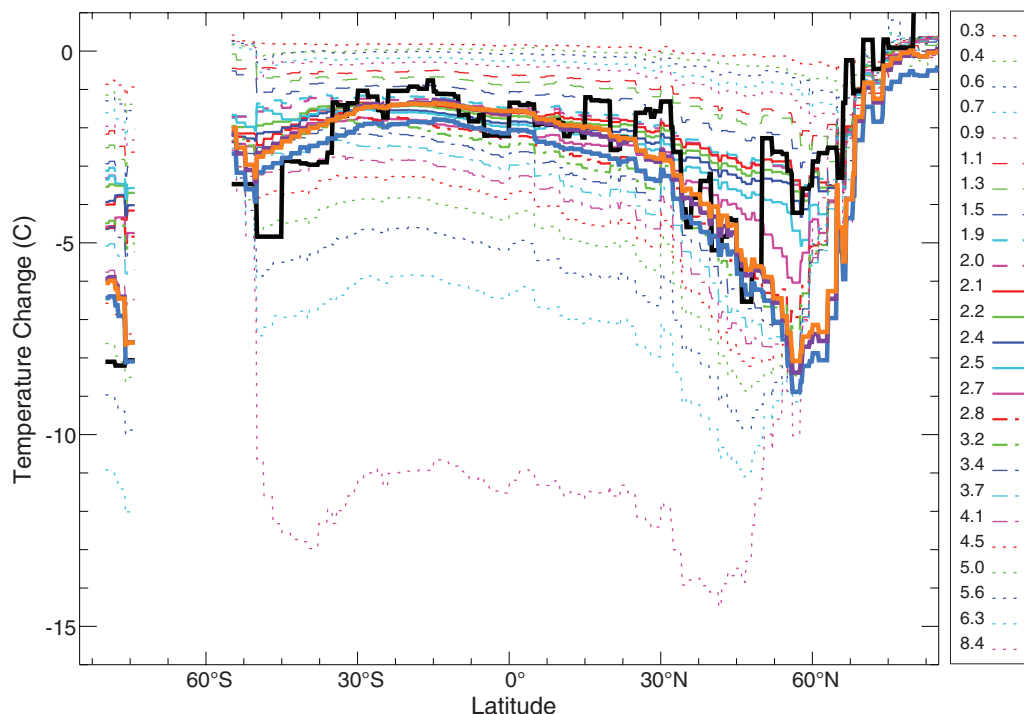
Fyke and Eby simulate the Last Glacial Maximum (LGM) with the same climate model—the

University of Victoria (UVic) Earth System Climate Model—but with a different version (2.9 versus 2.8) from that used in (*2*). Two important changes in the model and experimental design are likely to be responsible for most of the differences in simulated LGM surface temperature anomalies compared with (*2*) [see figure 2 in (*1*)]. First, Fyke and Eby modified heat diffusion in the atmosphere, which reduces heat transport in their LGM simulation. This leads to warmer temperatures in the tropics and colder temperatures at high latitudes. Second, they ignore dust forcing in the experimental design of the LGM simulation, which leads to generally warmer temperatures.

The modified heat transport is an interesting sensitivity experiment exploring structural uncertainties of the simple atmospheric energy-moisture balance model component. Although it seems that this modification improves the agreement with the reconstructions and may lead to larger permissible ECS<sub>2xC</sub> values than those estimated in (*2*), an unequivocal attribution and conclusion of its effect is hampered by the neglect of dust forcing in (*1*). Ample evidence from the paleo record shows elevated dust levels in the glacial atmosphere (*3*), and modeling studies have shown that dust radiative forcing influences climate (*4*) and estimates of climate sensitivity (*5*).

In a much-appreciated collaboration with Fyke and Eby, we have estimated the effect of dust forcing by calculating temperature anomalies from simulations in (*2*) with a model with similar ECS<sub>2xC</sub> (3.4 K) as that used in (*1*). Adding these anomalies to the model results in (*1*) (thick blue line in Fig. 1) results in too-cold temperatures over most of the tropics. The tropics are highly influential in the ECS<sub>2xC</sub> estimates in (*2*) because

**Fig. 1.** As figure 2 in (*1*), but including the effects of dust forcing (thick blue line) and without excluding data. The thick purple line, which is mostly obscured by the orange line, shows the dust forcing effects without the global mean. [Figure courtesy of M. Eby]



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of the large surface area covered with data [figure 1 in (2)]. This suggests that a model with smaller  $ECS_{2xC}$  than that used in (1) would be in better agreement with the observations. However, tropical temperatures in the model in (1) (with dust forcing considered) are significantly warmer than the models in (2) with similar  $ECS_{2xC}$  and are more similar to the models in (2) with lower  $ECS_{2xC}$  by about 0.8 K. This tentatively supports the conclusion in (1) that structural model uncertainties (in particular, formulations of atmospheric heat transport) may have led to systematic underestimation of  $ECS_{2xC}$  in (2). Further study with new ensemble model experiments, including the modified heat flux formulation and LGM dust forcing, are necessary to quantify the effect of heat flux uncertainties on the best  $ECS_{2xC}$  estimate.

Fyke and Eby also remove various data from the analysis. This is warranted in the few cases where the reconstructed ice sheet used in the LGM simulations incorrectly puts ice over areas where pollen records exist, because fair comparison with the model is not possible there. However, most data removed in (1), such as from the northern North Atlantic and Beringia, is based on more subjective criteria, such as model misfit. Differences between various sea surface temperature reconstructions in the North Atlantic were

extensively discussed by the Multiproxy Approach for the Reconstruction of the Glacial Ocean Surface (MARGO) group (6). Grid points for which different proxies do not agree have been assigned larger error bars. In the statistical method used in (2), these data points are given a lower weight and have little influence on the  $ECS_{2xC}$  estimate. Thus, proxy uncertainty was appropriately considered in (2). Fyke and Eby argue that dinocyst reconstructions from the North Atlantic should be discarded because they are warmer than those estimated from foraminifera species, but they do not discard dinocyst reconstructions from the North Pacific (7), which are anomalously cold relative to estimates based on Mg/Ca and foraminifera (8, 9). They also exclude data from Alaska, arguing that the UVic climate model cannot reproduce large spatial temperature gradients. Schmittner *et al.* (2) estimated model error objectively without removing data subjectively from the analysis. It is not surprising that removing data based on model misfit results in apparently improved model performance [as shown in the RMSE plots in the figure 2 insets in (1)]. We prefer the procedure recommended in the original MARGO data compilation (6), where all the data are retained and their uncertainties are rigorously accounted for when compared to models.

Finally, the simple metric (RMSE) used by Fyke and Eby does not permit probabilistic inferences. In particular, zonal averaging is problematic for statistical reasons (e.g., proper consideration of the reconstruction errors) and may obscure model error, and the RMSE does not consider spatial autocorrelation of the residuals, spatial error distribution of the reconstructions, or quantitative model error estimates. One feasible way forward would be to repeat the more complex study of (2) with model heat flux formulation uncertainties properly considered.

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22 March 2012; accepted 24 July 2012  
10.1126/science.1221634

## ANTHROPOLOGY

## Diversity Disregarded

N. J. Enfield

In a 1966 paper “The zoological perspective in social science,” the aptly named authors L. Tiger and R. Fox pitched the importance of biology to social anthropologists. “The fact that man is the animal which has relatively recently succeeded in dominating all others does not mean that he is therefore exempt both from being an animal and from being studied as such” (1). It is a simple enough point. Biologists commonly catalog detailed patterns of social behavior of different creatures, specifying for each species many of its ways of social life: patterns of mating, arrangements for rearing of young, structures of coalition and dominance, ways of distributing resources, and so on. So, for example, each primate species has an identifiable profile in the domain of sexual reproduction: pygmy marmosets practice polyandry (one female with multiple males) while hamadryas baboons practice polygyny (one male with multiple females) and gibbons practice nuclear-family style monogamy (2). If the lack of significant observed intraspecific variation allows such generalizations to be readily made about these primates, then one might expect the same for humans. We are, after all, a single species.

But the ethnographic record shows that such generalizations across the human species are not possible. Thus, for instance, in human family life around the world we observe just about every known primate arrangement (3), including the just-mentioned polyandry (e.g., in certain Tibetan groups), polygyny (e.g., in many African groups), and monogamy (practiced globally though far from universally). As cultural anthropologists have long known and shown, patterns of social behavior in humans display the kind of diversity that we see across species in other animals. Accordingly, Tiger and Fox argued not that ethology should take over social science but that there should be a marriage of the two disciplines. Just as social scientists need to learn from



**Visiting a spa.** Japanese macaques (*Macaca fuscata*) at Jigokudani hot spring.

biology, they suggested, biologists “have a lot to learn from students of the most complex social animal of them all” (1). Why, then, nearly 50 years later, is this needed marriage yet to be arranged?

In *Games Primates Play*, primatologist Dario Maestripieri (University of Chicago) argues that human social behavior is best understood in evolutionary context. The author’s expertise is in the social behavior of macaques, and he draws on his extensive experience and understanding of the dynamics of social life among nonhuman primates. Using concepts such as social dominance and cost-benefit trade-offs to analyze human relationships, he pursues the claim that the

social ways of humans are not particularly different from those of our closest evolutionary relatives. Maestripieri entertains the reader by juxtaposing portrayals of the social behavior of humans with that of other primates. So just as a macaque may adopt the strategy of behaving submissively to all his seniors,

waiting patiently for succession through the dominance ranks, a “good citizen” works her way to the top of a software corporation by being ultra-prosocial. Or just as a macaque may brazenly risk all by attacking the alpha male, so the “young Turk” in a research lab arrogantly challenges authority. It’s fun to read, but while the macaque stories are based on carefully documented scientific accounts, the human stories are fictional creations of

the author. Although the book is ostensibly about the science of human social behavior, most of what we are told about humans comes from personal anecdotes (“me-search,” as the author terms it), Hollywood gossip, or Maestripieri’s mind.

The author’s intuitions may be spot-on for the human groups he has observed, but the reader has no way to check. A more critical shortcoming is that from his convenience sample of data on human social relations, Maestripieri takes it as fact that “human beings around the world act the same way in similar social situations.” He dismisses the idea that human diversity might be important. After noting “behavior is variable,” by analogy with the essential properties of cats (“cats are cats”) and apples (“apples are apples”)

he submits that “humans are humans.” He fails to engage with the question of cultural diversity and to provide evidence to support his strongly universalist stance. Such shortcomings are surprising given that cognitive science is now beginning to seriously grapple with the implications of human diversity (4–7). Once we face such diversity head on, we come to very different conclusions. For example, as philosopher Jesse Prinz notes: “The investigation of our natural constitution should be directed at explaining human plasticity. We can call that the study of human nature, but the label is misleading. It carries with it the dubious idea that there is a natural way for human beings to be” (8).

To understand human sociality, a phylogenetic perspective is necessary but not sufficient. We must combine it with a historical perspective (9, 10). The observed diversity of human behavior arises from the combination of our extreme behavioral plasticity and the cumulative historical effects of social learning in human populations. This combination makes us radically different from other primates.

None of my criticism takes away from the importance of what Maestripieri wants to say about primate social relations—that we are evolved creatures with certain common problems and certain common strategies for solutions to those problems. But *Games Primates Play* addresses neither the empirical facts of human diversity nor their implications. To bring about the needed marriage between social science and biology, we need to focus on the relationship between a universal, evolved substrate for sociality (our high-

**Games Primates Play**  
An Undercover Investigation  
of the Evolution and Economics  
of Human Relationships  
by **Dario Maestripieri**  
Basic Books (Perseus), New York,  
2012. 320 pp. \$27.99, C\$31, £11.99.  
ISBN 9780465020782.

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grade social intelligence and strong propensities for cultural learning) and the important ways in which this substrate is embedded in, and sometimes even retooled by, culturally diverse ways of life.

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10.1126/science.1225365

#### PSYCHOLOGY

## What a Piece of Work Is Man

Barry Schwartz

About a century ago, psychology caught physics-envy flu, and behaviorism was born. If you can't measure it, you can't study it. You can't measure mental life, so study behavior. This rather pinched view of what it was possible to study (methodological behaviorism) grew into the view that it was all that was actually worth studying (radical behaviorism), and for almost half a century, that approach to understanding human beings dominated academic psychology. Though it left out much of what is most important about humans, behaviorism made substantial progress. In addition, it had built into it a focus on behavior—on action.

Then came the “cognitive revolution.” Investigators discovered that mind could be measured, and psychology was transformed. Much of psychology these days is the study of mind, whether in cognitive science, psychological neuroscience, decision science, affective science, or social cognition. The liberation from the tight methodological strictures

of behaviorism has produced insights and understanding that one couldn't have imagined in behaviorism's heyday.

But the cognitive revolution has brought collateral damage. In its enthusiasm for understanding mind, psychology largely lost interest in behavior. As a result, the study of what moves people to act in the world has been neglected. Action demands knowledge and motivation. Our understanding of knowledge grew ever more sophisticated and complex, but our understanding of motivation remained primitive. We'd assume that motivation is about seeking pleasure and avoiding pain. It's about seeking rewards and avoiding punishments. It's about meeting biological needs. End of story. Knowledge is complicated, but motivation is simple.

Well, no. Motivation is complicated, too. And E. Tory Higgins has spent a long and productive career studying that complexity. Now, he brings his work together in *Beyond Pleasure and Pain*. It is a magisterial work. Though its core structure revolves around Higgins' own theoretical insights and empirical findings, it is encyclopedic in scope, ranging into almost every corner of psychology, historical and modern. A careful reader of this book will get a picture of the best that psychology, in general, has to offer.

In brief (although the book resists easy



**Motivated.** Eva Risztov and Haley Anderson racing to the finish of the women's 10-km marathon swim at the 2012 Summer Olympics.

summary), Higgins's view is this: Of course, people pursue pleasure and avoid pain. Of course, much of what people do is as a means to valued ends. But people want more—much more—than pleasurable lives. People also want truth: they want to know what is real. As Higgins points out, Adam and Eve taught us this lesson when they ate from the tree of knowledge in Genesis. And people want control: they want to be effective in the world. And even when they pursue valued ends, the means matter—both what people do and how they do it (“God loveth adverbs,” the saying goes). Moreover, these various motives interact in complex ways. They don't simply add

### Beyond Pleasure and Pain How Motivation Works

by E. Tory Higgins

Oxford University Press,  
Oxford, 2012. 568 pp. \$69.95,  
£45. ISBN 9780199765829.

together or substitute for one another. And they are manifested differently in different people and by the same people in different contexts. One does not automatically enhance learning by making learning fun—by making it pleasurable.

Nor does one enhance learning by making it materially rewarding (a fact amply demonstrated by the failure of recent efforts to improve student performance with often substantial material incentives).

People are complicated, motives are complicated, and the key to successfully motivating people to act in desired ways is in finding or creating a fit between different motives, different individual predilections, and different contexts. The notion of “fit” is a crucial component of Higgins' account. So also is what he calls “regulatory focus”—the orientation either to promote good results or to prevent bad ones. People differ in which of these two orientations dominates their activities, but even people with a dominant promotion focus are in prevention mode some of the time.

Although targeted for nonacademics and gracefully written, the book is not an easy read. Higgins refuses to oversimplify. It takes him more than 400 pages to tell his story (with an additional 100 pages of notes and references). And that's too bad. Because anyone who tries to manage a workforce and thinks that getting productivity is just a matter

of finding the right system of financial incentives should read this book. Anyone who teaches and thinks that getting mastery from students is just a matter of finding the right incentives should read this book. And anyone who works in healthcare and thinks that getting people to live healthier lives is just about finding an effective way to give them the relevant information should read this book. In short,

nearly anyone who works with other people should read this book.

But most of the people who need to read *Beyond Pleasure and Pain* won't. They want simple answers, quick solutions. We have spent years thinking that there are simple solutions to life's complex problems, that there are one-size-fits-all magic bullets to promote healthy, informed, productive lives. Well, Shakespeare was right, and we've been wrong. Humans are quite a complex piece of work. And Higgins does a masterful job of both revealing and explaining that complexity.

10.1126/science.1227731

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## SCIENCE AND INDUSTRY

# Federal Laboratory–Business Commercialization Partnerships

Gina K. Walejko,\* Mary E. Hughes, Susannah V. Howieson, Stephanie S. Shipp

U.S. federal laboratories, government-owned and either government-operated (GOGO) or contractor-operated (GOCO), spent \$40.4 billion on research and development (R&D) in 2009. This represents 30% of U.S. federally funded R&D obligations (1). Federal labs offer unique resources, including multidisciplinary teams of scientists and engineers, large and complex facilities, and ability to work on classified research. Given these resources and increasing calls for greater returns on federally funded R&D investment, the U.S. government has solicited the labs to engage and facilitate partnerships with businesses to produce commercial technologies [e.g., (2)].

We discuss challenges to such partnerships and the strategies that federal labs have used in attempts to overcome them (3). Previous studies of such efforts are outdated and limited to particular labs. Our current analysis relies on self-reported information; many efforts have not yet been rigorously evaluated. Our focus is on the transfer of federal lab technologies to market through a variety of pathways, including joint research projects between industry and labs under cooperative research and development agreements (CRADAs), as well as patents, licenses, and creation of start-ups (see the photo). Federal labs transfer technology in other ways, including published research dissemination, researcher training, and standards development.

## Visibility, Differences, Constraints

Many businesses do not know that federal labs exist or are not familiar with their resources. Many labs' Web sites do not list inventions available for licensing and only sparsely describe their research. This lack of visibility is especially difficult for small businesses that do not have resources to explore lab offerings. One approach is to increase the federal labs' online presences. The Department of Energy's (DOE's) Energy Efficiency and Renewable Energy (EERE) office launched a portal for DOE lab patents related



to its research focus (4). The National Institutes of Health (NIH) lists available licensing opportunities (5) and developed an electronic catalog for companies to find unpatented biological materials (6). The Federal Chief Information Officer and others have been directed to create a public database for federally owned inventions (2). The Interagency Working Group for Technology Transfer (IWGTT) and the Federal Laboratory Consortium for Technology Transfer (FLC) (7) have also worked to raise the visibility of the federal labs.

Differing timelines and cultures of businesses and federal labs remain as challenges (8–10), and familiarization is a bilateral issue. Companies may have complex demands that slow negotiations. Rules and regulations may hinder federal labs' abilities to partner with companies (3). Federal labs are undertaking steps to overcome legal hurdles faced in partnering. NIH (11) and DOE (12) labs have developed e-mail and other streamlined agreements to reduce negotiation times. DOE is examining best practices (13) and has found wide variation in the time to implement a CRADA across DOE labs (14). Partnership intermediaries also serve as brokers to manage business and lab expectations. They

U.S. federal laboratories face challenges to partnerships that result in commercial technologies.

**A lithium-ion battery for the Chevy Volt automobile.** Produced by LG Chem, which licensed cathode technology from the U.S. Department of Energy's Argonne National Laboratory.

help businesses assess early technologies and structure and negotiate agreements for working with labs, services that may be especially important for small firms (3). For example, the U.S. Department of Agriculture's Agricultural Technology Innovation Partnership is a network of local, state, and regional economic development organizations that seek potential business partners for labs and assist negotiations (15).

## Incentives, Uncertainties, Unawareness

The Stevenson-Wydler Technology Innovation Act of 1980 and later amendments, the counterparts to the Bayh-Dole Act that addressed universities, made technology transfer the responsibility of federal lab researchers, consistent with their missions (16). Although evaluation of technology transfer activities in researcher performance reviews has been required by law since 1986, it is implemented by only some federal labs (3, 17). Also, federal lab researchers do not receive the same incentives to commercialize as some university researchers. Royalty payments for GOGO lab researchers are capped at \$150,000 per year, whereas university researchers and GOCO employees typically do not face such restriction (18–20). Providing sufficient incentives to GOGO employees while avoiding potential conflicts of interest is a complex issue, one being examined by the IWGTT (21).

Federal lab researchers may be unaware of how to develop industry partnerships. Although a bigger problem in the past, lack of business acumen by technology transfer staff and researchers may impede partnerships with companies. Recognizing the importance of broad training for successful technology transfer personnel and researchers, some technology transfer offices hire staff with marketing or business development expertise. Some labs attempt to increase the business culture of their researchers through workshops and formal training that educate researchers to identify potential partners (3).

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Technologies developed at labs are frequently early-stage and require work to determine commercial feasibility. Scaling up technologies, understanding how they incorporate into technical systems, and performing proof-of-concept research require resources and business stakeholders. In this way, federal labs are similar to university labs, although challenges in transitioning technologies are exacerbated by the difficulty of GOGO employees in consulting and starting businesses, in part due to conflict-of-interest rules (3).

To overcome these obstacles, several federal labs are exploring avenues for businesses to develop early-stage technologies into commercially viable products. Since 2008, the

applied research with the goal of contributing to economic development. In 2008, almost two-thirds of their €1.3 billion research budget came from contracts with companies (29). Germany also maintains 18 Helmholtz Centers with long-term research mission goals (30) that receive two-thirds of their funding from the public (31). However, suggesting international labs as models may be futile, as past attempts at formal U.S. government-business partnerships, including lab partnerships, have been criticized (32, 33).

Increasingly, federal labs are called upon to contribute to economic development, sometimes via partnerships, yet technology transfer is just one lab function and can be viewed as an unfunded mandate or tangen-

## Many businesses do not know that federal labs exist or are not familiar with their resources.

National Institute of Standards and Technology (NIST) has used a portion of Small Business Innovation Research funds to promote development of lab inventions by small businesses (22). This program is being implemented by other federal labs. Others are working with intermediaries to provide technology maturation funds. Maryland Technology Development Corporation launched an initiative to fund small businesses to commercialize technologies that meet Department of Homeland Security and U.S. Army Medical Research and Materiel Command needs (23).

Federal labs have developed ways to identify, protect, and transfer technologies related to their core missions since the establishment of technology transfer offices in the 1980s. However, unexpected research results may have applications far removed from the lab mission. Some labs are attempting to discover these connections. DOE EERE has an entrepreneur-in-residence program that places business people in DOE labs to conduct market assessments, identify commercial opportunities, and develop business cases for technologies (24). Los Alamos and Pacific Northwest National Laboratories host business student “technology scouts” to examine the commercial potential of laboratory technologies (25).

### Looking Abroad and Ahead

Policy-makers occasionally reexamine the roles of U.S. federal labs but historically do not look at international models (26–28). As an example, one of Germany’s Fraunhofer Institutes’ explicit missions is to perform

tial to labs’ missions (34). There is no empirical evidence to suggest that previously mentioned strategies strengthen economic development more than if resources had been invested elsewhere. Thus, policy-makers should give consideration to how economic development fits within the federal labs’ missions and how these labs fit within the broader context of federally funded R&D. Strategies to strengthen federal lab–business commercialization partnerships should be subject to formal, empirical evaluation that considers the multiple functions and diversity of federal labs and their multiple functions, including mission and management structures.

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**Acknowledgments:** We thank P. Singerman, P. Zielinski, and G. Anderson at NIST and S. Koonin, N. Gupta, S. Jonas, A. T. Brenner, D. Holmes, and E. Shyu of IDA STPI. This research was sponsored by the Department of Commerce (DOC). Opinions expressed are those of the authors alone and do not reflect positions of IDA STPI or DOC.

10.1126/science.1221962

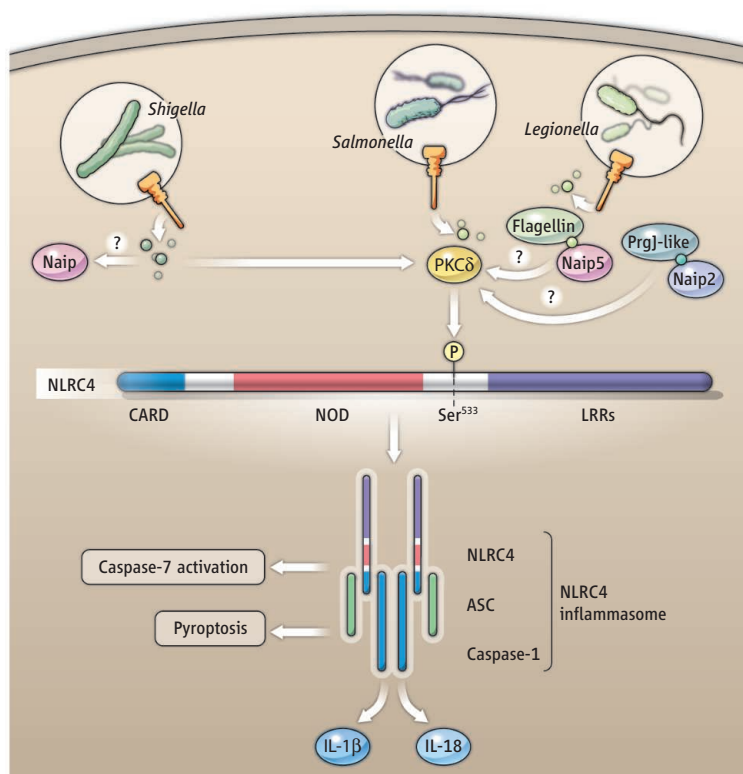
## IMMUNOLOGY

## Orchestrating Inflammasomes

Luigi Franchi and Gabriel Núñez

The initial sensing of invading pathogens by the human immune system is largely accomplished by host pattern-recognition receptors in phagocytes (such as macrophages) that detect conserved microbial components or endogenous host molecules generated after cellular injury (1). This launches a signaling pathway called the inflammasome, causing phagocytes to release cytokines that harness immune responses to fight infection. There are several different types of inflammasomes and the mechanistic details of their assembly are still being elucidated. Some are triggered by the activation of the Nod-like receptor (NLR) family of intracellular receptors. Qu *et al.* (2) have recently identified the phosphorylation of NLRC4 as a critical step in its assembly into an activated inflammasome.

An inflammasome is a multiprotein complex that turns on the protease caspase-1. Caspase-1 cleaves pro-interleukin-1 $\beta$  (IL-1 $\beta$ ) and pro-IL-18 into active forms. Upon release from phagocytes, IL-1 $\beta$  and IL-18 act on neighboring cells to orchestrate immune responses for pathogen clearance (3). NLRC4 is activated upon infection by several Gram-negative bacteria, including *Legionella pneumophila*, *Salmonella typhimurium*, and *Shigella flexneri* (3). This requires the presence of a type III or IV secretion system that translocates bacterial virulence factors as well as flagellin or PrgJ-like rod proteins into the host cytoplasm (4–6). Although flagellin or rod proteins activate the NLRC4 inflammasome, the underlying molecular mechanism has been poorly understood.



**Assembly steps.** Infection of macrophages with the Gram-negative bacteria activates caspase-1 through the NLRC4 inflammasome. Bacterial flagellin or PrgJ-like rod proteins are delivered into the cytosol through type III and IV secretion systems (orange) and are recognized by Naip5 and Naip2, respectively. *Shigella* activates the NLRC4 inflammasome through an unknown microbial product. Infection activates PKC $\delta$  and possibly other kinases that phosphorylate (P) NLRC4, a step that is critical for inflammasome assembly and activation. Domains in NLRC4 are shown (CARD, caspase-recruitment domain).

To identify steps in NLRC4 inflammasome activation, Qu *et al.* genetically engineered mice to express a tagged form NLRC4 that could be analyzed by mass spectrometry. This approach revealed that *Salmonella* infection induces NLRC4 phosphorylation at Ser<sup>533</sup>. *Salmonella* mutants deficient in flagellin or PrgJ could not induce Ser<sup>533</sup> phosphorylation. Inhibition of caspase-1 did not affect phosphorylation, indicating that the modification of NLRC4 is an early event upstream of protease action. Using biochemical approaches, Qu *et al.* identified protein kinase C  $\delta$  (PKC $\delta$ ) and p21-activated kinase 2 (PAK2) as enzymes that phosphorylate NLRC4 at Ser<sup>533</sup>. Further genetic studies suggested that PKC $\delta$  is the major kinase responsible for inflammasome assembly and activation (see the figure).

How is PKC $\delta$  activated in response to bacterial infection? Previous work identi-

A multiprotein structure in immune cells requires phosphorylation of a constituent to propel its assembly and activation for clearing bacterial infection.

fied Naip2 and Naip5, two related members of the NLR family, as critical factors in the activation and assembly of the NLRC4 inflammasome through their interaction with flagellin and rod proteins (7, 8). The finding of Qu *et al.* raises questions about how Naip proteins are linked to PKC $\delta$  activation or whether NLRC4 phosphorylation plays a role in their recruitment to the inflammasome. In addition, the involvement of PKC $\delta$  opens the possibility that pathogens may target this kinase to inhibit the NLRC4 inflammasome.

Qu *et al.* show that a mutation that mimics phosphorylated Ser<sup>533</sup> increases the ability of the NLRC4 inflammasome to induce pyroptosis, a caspase-1-dependent form of macrophage cell death, suggesting that NLRC4 phosphorylation can induce inflammasome activation. However, the molecular mechanism by which phosphorylation promotes activation remains unclear. Ser<sup>533</sup> is evolutionarily conserved and located between the central nucleotide-binding oligomerization domain (NOD) and the carboxyl-terminal leucine-rich repeats (LLRs) of NLRC4. In the absence of any stimulation, NLR proteins are thought to be in an autoinhibited state conferred by the amino-terminal end of the LRR domain and relieved upon microbial stimulation (9, 10). Perhaps phosphorylation of Ser<sup>533</sup> provides a positive activating signal or relieves the self-inhibited state of NLRC4.

The study by Qu *et al.* highlights the importance of posttranslational modification as an indirect mechanism for linking microbial molecules to NLR activation. Indeed in plants, nucleotide-binding–leucine-rich repeat (NB-LRR) proteins, which are structurally homologous to NLRs (11, 12), recognize pathogen-derived molecules and activate host defense responses (13). Many plant

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NB-LRR proteins monitor pathogen presence through the modification of accessory host proteins, which is induced by pathogen effectors (11, 12). Future studies will determine whether modification of NLRs or the direct interaction between NLRs and their respective ligands activates inflammasomes other than NLRC4.

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**Acknowledgment:** The authors declare no competing financial interests.

10.1126/science.1229010

#### CELL BIOLOGY

## Staging Membrane Fusion

Josep Rizo

Upon arrival of a nerve impulse, neurons release neurotransmitters contained within synaptic vesicles to transmit signals to other neurons, thus enabling a myriad of neural functions. Neurotransmitter release is mediated by the soluble *N*-ethylmaleimide-sensitive factor attachment protein receptor (SNARE) proteins synaptobrevin, syntaxin-1, and SNAP-25, which govern the fusion of synaptic vesicles with the plasma membrane. Assembly of the tight complex formed by the SNAREs is believed to provide the energy for fusion (1, 2) and to occur in steps, zippering from the amino terminus to the carboxyl terminus (3) (see the figure). Biophysical data in solution (4, 5) and studies of SNARE complexes anchored at separate surfaces using surface force apparatus (6) or atomic force microscopy (7) supported this notion and provided insights into the zippering forces. However, fundamental questions remained about the energy land-

scape and the overall free energy of SNARE complex assembly. On page 1340 of this issue, Gao *et al.* (8) combine a clever design with a high-tech optical approach to dissect neuronal SNARE complex assembly into three steps and to determine the associated free energies. This remarkable technical achievement has profound implications to understand the mechanism of neurotransmitter release.

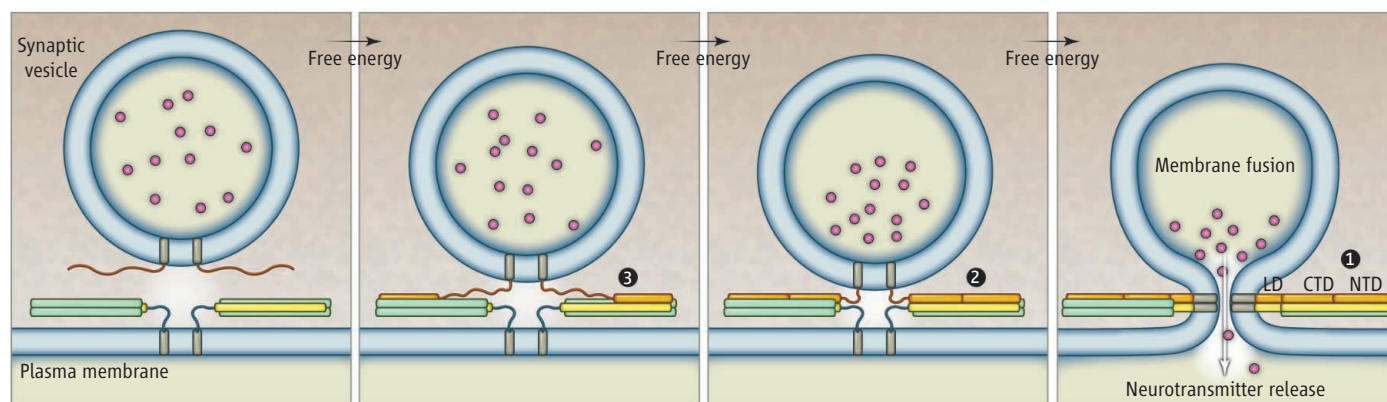
Gao *et al.* used the high force resolution of dual-trap optical tweezers to study single SNARE complexes linked to separate beads via the carboxyl termini of synaptobrevin and syntaxin-1, while their amino termini were cross-linked. Force-extension curves showed reversible transitions corresponding to two interconversions between defined states and providing their relative free energies. The first transition (extension  $\sim 3$  nm; free energy  $8 k_B T$ , where  $k_B$  is Boltzmann's constant and  $T$  is temperature) involves interconversion between fully assembled SNARE complex and an intermediate where the synaptobrevin linker domain is unfolded (states 1 and 2, respectively; see the figure). This was an unexpected, key find-

Optical tweezers reveal how single neuronal SNARE complexes assemble in three stages to force synaptic vesicle fusion and neurotransmitter release.

ing that emphasizes the high sensitivity of this approach. The second transition (extension  $\sim 7$  nm; free energy  $28 k_B T$ ) entails formation of another intermediate where the synaptobrevin carboxyl-terminal domain is unfolded (state 3). Additional experiments in which the SNARE complex was pulled from the amino terminus yielded a free energy of  $35 k_B T$  for disassembly of the amino-terminal domain (with carboxyl-terminal domain and linker domain folded). The individual free energies measured for assembly of the amino-terminal domain or the carboxyl-terminal domain are higher than that of the strongest coiled-coil protein reported to date, but even more remarkable is the extraordinary overall free energy of SNARE complex formation, estimated at  $65 k_B T$  [see (8)].

How are the energies of the different zippering steps applied to induce membrane fusion? Some reconstitution experiments suggested that a single SNARE complex is sufficient for fusion (9, 10), in agreement with the free energy of zippering and the estimated energy required for fusion ( $\sim 50 k_B T$ ) (11). However, this estimate has a large uncertainty,

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**Generating force for membrane fusion.** The states of the SNARE complex derived by Gao *et al.* are numbered. Helical regions are cylinders. The soluble parts of these SNAREs are colored (syntaxin-1, yellow; SNAP-25, green; synaptobrevin, orange). The transmembrane domains (dark gray) were not included in the study. The synap-

tic vesicle and plasma membranes are believed to approach and fuse as the SNARE complex assembles. The three synaptobrevin domains are amino-terminal domain, NTD; carboxyl-terminal domain, CTD; and linker domain, LD. LD may be normally unstructured but becomes helical in state 1.

and a substantial amount of the zippering energy may be dissipated while bringing the membranes together. Hence, it is plausible that assembly of the amino-terminal domain generates state 3, and what actually causes fusion is assembly of the carboxyl-terminal domain and linker domain, perhaps augmented by binding between the transmembrane domains and/or linker domain-membrane interactions.

A different scenario is suggested by other reconstitution data indicating that multiple SNARE complexes can be formed between membranes without inducing fusion (12). This finding could be explained if considerable repulsion between two membranes occurs only below ~4 nm (the intermembrane distance in state 2) and most of the zippering energy is used to produce state 2, yielding only the  $8 k_B T$  of linker domain zippering available for fusion. These observations suggest the possibility that the energy of linker domain zippering, though substan-

tial, is insufficient for fusion and needs to be augmented by factors such as the  $\text{Ca}^{2+}$  sensor synaptotagmin-1, which can also bridge two apposed membranes and might help bending them to initiate fusion (13). This feature could explain the  $\text{Ca}^{2+}$  dependence of synaptic vesicle fusion and would not be shared by other forms of membrane fusion that are  $\text{Ca}^{2+}$  independent.

The energy of carboxyl-terminal domain assembly, and perhaps even that of amino-terminal domain assembly, could be applied more efficiently to bend the membranes and induce fusion if the SNARE complex assembles while bound to bulky proteins such as Munc18-1 and/or Munc13s, which play crucial roles in neurotransmitter release. This could prevent the membranes from coming too close, thus favoring application of a torque by the SNAREs on the membranes (2). Repulsion between the SNARE complex and the membranes, or between the membranes

at close distances, could also play a similar role. Moreover, multiple SNARE complexes could cooperate in fusion. Clearly, much research will be required to explore these ideas. Undoubtedly, the approach developed by Gao *et al.* will continue producing key advances in the field.

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10.1126/science.1228654

## NEUROSCIENCE

# The Emerging Biology of Autism Spectrum Disorders

Matthew W. State<sup>1</sup> and Nenad Šestan<sup>2</sup>

Autism spectrum disorders (ASD) are a genetically and phenotypically heterogeneous group of syndromes defined by fundamental impairments in social reciprocity and language development accompanied by highly restrictive interests and/or repetitive behaviors. Recent advances in genetics, genomics, developmental neurobiology, systems biology, monogenic neurodevelopment syndromes, and induced pluripotent stem cells (iPSC) are now offering remarkable insights into their etiologies and converging to provide a clear and immediate path forward from the bench to the bedside.

Leading the charge has been the emergence of reliable genetic findings. Multiple studies have confirmed that rare and de novo point mutations and submicroscopic variations in chromosomal structure contribute to a considerable number of cases and have identified a growing number of specific genomic intervals and genes conferring risks (1–9). These advances provide a critical foundation for the development of a

more refined understanding of the biological underpinnings of ASD. The earliest findings in the genetics of idiopathic (nonsyndromic) autism highlighted the role of synaptic adhesion molecules and postsynaptic density proteins (1, 10). A set of newly discovered ASD proteins (see the figure) expands this view, highlighting a role for chromatin modifiers (CHD8), and DNA binding proteins (POGZ), ion channels (SCN2A), microtubule-associated proteins (KATNAL2), neurotransmitter receptors (GRIN2B), and phosphorylation-regulated tyrosine kinases (DYRK1A) (5–9).

As success in discovery has accelerated, the number of genes predicted to carry risk for ASD has steadily increased, now reaching well into the hundreds (5–9), with no single locus accounting for more than 1% of cases. This “many-to-one” relationship suggests that future studies need to go beyond isolated molecular dissections of single mutations. Another surprising and conceptually challenging observation from recent genetic studies has been the considerable overlap of risks for distinct disorders. Identical highly penetrant variants in different individuals carry large effects but for a wide range of outcomes,

Expression patterns of the diverse genes disrupted in autism spectrum disorders in the developing brain give a fresh perspective on the underlying biology.

including, but likely not limited to, ASD, epilepsy, intellectual disability, and schizophrenia. This “one-to-many” phenomenon, combined with the biological pleiotropy of genes that have so far been implicated in ASD and the presence of core phenotypes that are distinctly human, such as impairments in language development, make the study of ASD in model organisms especially challenging. While modeling mutations in animals or cell culture will reveal perturbations in conserved biological pathways, the key challenge will be to determine which molecular, cellular, and neural circuit-level phenotypes are particularly relevant for ASD.

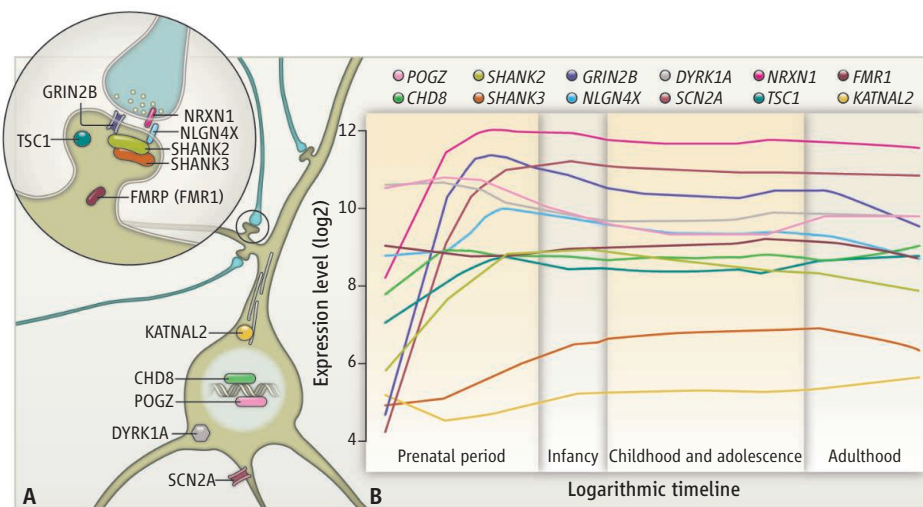
Ironically, the staggering degree of locus heterogeneity may hold the key to translating genetic findings into a new generation of treatments. The growing set of newly discovered ASD genes should provide a powerful means to use convergence among molecular pathways and cellular processes to identify relevant biological and therapeutic targets. As gene discovery progresses for schizophrenia, epilepsy, and other neurodevelopmental and neuropsychiatric disorders, the ability to study both convergence and divergence of mechanism across conditions will become

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increasingly feasible. There is already convincing evidence that molecular pathways converge in ASD (9, 10). What is particularly exciting, however, is the new-found opportunity to address not just the question of which molecules and pathways intersect but to specify when and where these events occur within the developing human brain.

The recent emergence of comprehensive maps of spatiotemporal gene expression (11) in the human brain, the ability to construct similar maps of gene-regulatory interactions and chromatin states, and the availability of a growing list of definitive ASD point mutations sets the stage for a powerful developmentally informed approach to studying ASD biology. For example, genes conferring risk can be assessed for spatially and temporally defined gene coexpression and coregulatory networks during human brain development. The identified networks can be evaluated with respect to molecular, anatomical, and developmental convergence, and mechanistic hypotheses can be generated and tested. Confirmation at the bench can leverage model systems, postmortem human tissue, and iPSC-derived neural cells, including isogenic lines carrying engineered mutations and cells generated from patients carrying the mutation(s) of interest. Overall, this type of integration offers immediate opportunities to define relevant molecular and cellular processes and, as more and more genes are identified, will increasingly point to higher-level neural system properties relevant to ASD.

In fact, the available published data on ASD gene expression in the developing human brain already points to some intriguing etiological hypotheses and plausible explanations for the observation that a single genetic risk variant can lead to highly divergent phenotypes, including autism and schizophrenia. Many of the ASD genes noted above exhibit distinctive spatiotemporal expression patterns in the developing brain, including dramatic increases in the cerebral cortex during mid-gestation (see the figure), a developmental period crucial for the formation of early neural circuits (11, 12). The assembly of related cortical neural circuits progresses in an orderly spatiotemporal pattern such that, in general, neurons in the anterior regions are chronologically older, and form synapses earlier, than neurons in the posterior regions. Indeed, signs of early cortical neuronal differentiation and synapse formation are present in the regions of the early and mid-fetal prefrontal and temporal cortices (11, 12) that ultimately give rise to circuits underlying executive control, social affective processing, and language—all functions that are altered



**Developmental neurobiology of ASD risk genes.** (A) Diverse subcellular distribution and pleiotropic roles for syndromic and idiopathic ASD proteins. (B) Expression profiles of select previously established and newly identified ASD genes during development of the human neocortex. See supplementary materials for methods.

in ASD (13). These early regional differences in the timing of synaptogenesis may help explain why the ontogenetically older circuits involved in these processes are particularly vulnerable in ASD, whereas other cortical processes, such as vision, are less affected. The rarity and functional immaturity of nascent synapses in the early and mid-fetal cortex may make them especially susceptible to perturbed function of ASD-related genes, which appear to be dynamically regulated during the same developmental window.

Several lines of evidence indicate that cortical areas and their circuits mature at different rates during postnatal development (14). Higher-order association cortices, including prefrontal and temporal cortices, do not fully mature until late adolescence and early adulthood (14), and some of their maturational trajectories are altered in ASD and schizophrenia (13, 14). Their extended period of maturation may increase the sensitivity of the ontogenetically older frontal and temporal circuits involved in executive control, social affective processing, and language, to both ongoing alterations in the molecular landscape, and interceding environmental insults. In short, the identical genetic risk could lead to variable phenotypes via early developmental and ongoing functional alterations in temporally defined molecular interactions in neural circuits that show both early vulnerability and an extended period of maturational sensitivity.

Although integrated genetic, molecular, and circuit-level analyses are critical for identifying more refined mechanistic hypotheses, important questions will remain unresolved. For instance, what is the nature of the male predominance in ASD? How and why do particular individuals show resil-

ience in the face of highly penetrant genetic risks? What roles do genetic background, somatic mutation, epigenetic modifications, the microbiome, environmental factors, and stochastic events play in determining the emergence and trajectory of symptoms? Fortunately, as the overall genetic landscape of ASD becomes clearer, these difficult questions appear increasingly tractable.

The most pressing issue for patients, families, and physicians at present is what recent findings portend for prevention and treatment. In this regard, demonstrations that aspects of the phenotypes accompanying monogenic neurodevelopmental syndromes are reversible in model organisms (10) provides promise that key features of human neurodevelopmental disorders involve the contribution of dynamic, and therefore potentially treatable, derangements in neural function. Moreover, although the picture of one mutation leading to a diverse array of disorders is conceptually challenging, the model we have proposed suggests that there may be useful analogies to treatment strategies from other areas of medicine. For example, heart disease and stroke prevention both rely in part on the management of hypertension. It may well be that ASD and schizophrenia will increasingly be thought of in a similar light, reflecting divergent manifestations of a shared pathophysiological liability. This would further underscore the importance of clarifying the nature of the molecular and neural circuit-level perturbations underlying these disorders. It would also suggest that future treatment trials will need to be organized around these shared mechanisms, as opposed to traditional psychiatric diagnostic categories. Finally, while the molecular diversity underlying ASD presents a con-



siderable challenge in the search for convergence, it may well also portend, just as it has in cancer, the development of both more personalized and more effective therapies.

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**Acknowledgments:** This work was supported by Overlook International Foundation (M.W.S. and N.S.); the Simons Foundation (M.W.S.); and the National Institutes of Health (U01MH081896 and R01NS054273 to N.S.; R01MH081754, P50MH081756, and RC2MH089956 to M.W.S.).

#### Supplementary Materials

[www.sciencemag.org/cgi/content/full/337/6100/1301/DC1](http://www.sciencemag.org/cgi/content/full/337/6100/1301/DC1)

10.1126/science.1224989

## MATERIALS SCIENCE

# Building Research Equipment with Free, Open-Source Hardware

Joshua M. Pearce

Most experimental research projects are executed with a combination of purchased hardware equipment, which may be modified in the laboratory and custom single-built equipment fabricated in-house. However, the computer software that helps design and execute experiments and analyze data has an additional source: It can also be free and open-source software (FOSS) (1). FOSS has the advantage that the code is openly available for modification and is also often free of charge. In the past, customizing software has been much easier than custom-building equipment, which often can be quite costly because fabrication requires the skills of machinists, glassblowers, technicians, or outside suppliers. However, the open-source paradigm is now enabling creation of open-source scientific hardware by combining three-dimensional (3D) printing with open-source microcontrollers running on FOSS. These developments are illustrated below by several examples of equipment fabrication that can better meet particular specifications at substantially lower overall costs.

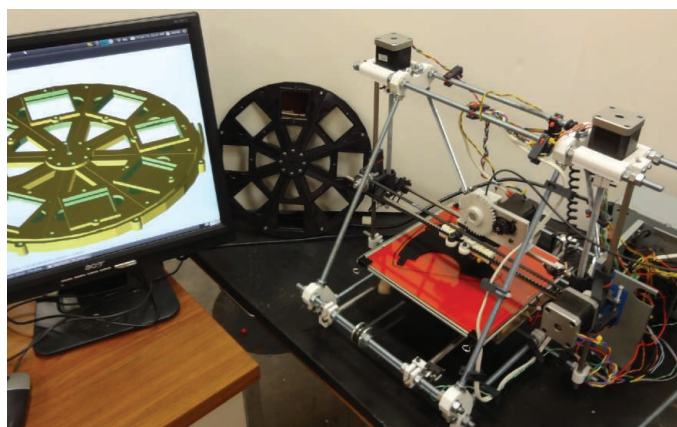
The FOSS movement emerged as a decentralized, participatory, and transparent system to develop software, in contrast to commercial software, which tends to be written anticipating user needs and does not allow modifications to the code, which is often proprietary (2). Although FOSS is a collaborative effort driven by

user demands, this decentralized innovation process is still efficient and has been implemented in areas such as nanotechnology (3) and medicine (4), and the open and collaborative principles of FOSS have been readily transferred to hardware (5). A key enabling open-source hardware project is the Arduino electronic prototyping platform (6–8). The \$20 to \$30 Arduino is a versatile yet easy-to-learn microcontroller that can run a number of associated scientific instruments, including Arduino Geiger (radiation detector), pHduino (pH meter), Xoscillo (oscilloscope), and OpenPCR (DNA analysis). However, Arduino's most impressive enabling application is 3D printing. Open-source 3D printers can perform additive-layer manufacturing with polymers, ceramics, and metals. Such approaches have been popular in microfluidic lab-on-a-chip architectures, where flow paths are created layer by layer, but are adaptable to

a much wider array of devices.

The most popular fabrication tool is the RepRap, named because it is a partially self-replicating rapid prototyping machine. Currently, the <\$1000 RepRap can fabricate about 50% of its own parts from acrylonitrile butyl styrene or polylactic acid polymers with no postprocessing and a 0.1-mm spatial precision. This ability for self-replication has resulted in an explosion of both RepRap users and evolutionary design improvements (9). Scientists with access to RepRaps have found many examples where it is less expensive to design and print research tools rather than buy them. A number of simple designs are flourishing in Thingiverse, a free and open repository for digital designs of physical objects (10). These include single-component prints such as vial racks (thing:25080), Buchner funnels (thing:25188), and micro-titer plates (thing:11621). 3D printers have also been used to print custom chemical reactionware (11). For example, 3D printers can be outfitted with syringes to print with materials like acetoxysilicone to quickly make reactionware capable of in situ spectroelectrochemistry or easily alter reactor architecture to gauge the effects on chemical synthesis (11).

The 3D printers can also be coupled with existing hardware tools such as the portable cell lysis device for DNA extraction (thing:18289), a 3D printable adapter that converts a Craftsman automatic hammer into a bead grinder for use with DNA extraction, or the DremelFuge chuck (thing:1483), a printable rotor for



**Factory for one.** A parametric (easily customized) filter-wheel holder is shown in the OpenSCAD program on the monitor (left), with the completed inside of the Arduino-controlled automated filter wheel (center). An Arduino-controlled RepRap 3D printer (right) is printing out a component of a case design. All of the hardware and software for both the filter wheel and the RepRap are open source.

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centrifuging standard microcentrifuge tubes and miniprep columns. These combination devices can radically reduce research costs. For example, the DremelFuge can be used in the laboratory or the field as an inexpensive centrifuge demonstrated to be effective up to 33,000 rpm or 52,000g. The price is ~\$50—primarily for the Dremel drill—compared with commercial centrifuge systems, which cost a few hundred dollars (12).

The most aggressive research savings can come from coupling Arduinos with 3D printers to make full open-source scientific hardware. Consider the Arduino-controlled open-source orbital shaker (thing:5045) used for mammalian cell and tissue culture and bench-top science. The <\$200 open-source orbital shaker fits inside a standard 37°C/5% CO<sub>2</sub> cell incubator and replaces commercial versions that start at more than \$1000. As the scientific tools that are open sourced gain complexity, the cost differential becomes even more substantial. For example, it is now possible to make a <\$50 customizable automated filter wheel (thing:26553) that replaces \$2500 commercial versions.

For any given project, there may still be drawbacks to open-source 3D digital fabrication versus buying. Open-source scientific hardware is still at an early stage of the evolutionary process. Today, most major equipment is too complex to build in this manner (e.g., an entire nuclear magnetic resonance spectrometer versus a sample holder for one) or requires specialized materials that need to be fabricated in dedicated systems (e.g., ultrahigh vacuum semiconductor deposition). Commercial equipment may have longer lifetimes and, for instrumentation, may have better statistical validation of calibrations. If a new design is needed, it may often prove faster to buy than build. However, as more designs are shared, the level of complexity of open-source scientific hardware will expand rapidly. Not only can the scientific community enjoy immediate cost reductions by building and sharing but also, as with software, the costs of commercial versions will decrease because of price competition. We are on the verge of an era where low-cost, but highly sophisticated, scientific equipment can be put into the hands of the pub-

lic and amateur scientists everywhere, while driving down the costs of research tools at our most prestigious laboratories (12).

#### References and Notes

1. Free and open-source software is computer software that is available in source code (open source) form and that can be used, studied, copied, modified, and redistributed without restriction, or with restrictions that only ensure that further recipients have the same rights under which it was obtained (i.e., free).
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10.1126/science.1228183

#### ECOLOGY

## When Paths to Cooperation Converge

Thomas N. Sherratt<sup>1</sup> and Gilbert Roberts<sup>2</sup>

Observations of cooperation range from human philanthropy to fiddler crabs leaving their territories to help neighbors thwart an intruder (1). Two of the best-known explanations for such cooperation are direct reciprocity (2), in which cooperation evolves as a conditional strategy over repeated interactions, and population structuring (3), in which cooperators associate disproportionately with cooperators. However, many systems have the potential to generate cooperation through both of these routes; for example, common murrelets (see the figure) regularly preen both their mates and close colony neighbors over repeated interactions. How might these routes to cooperation interact? In a recent paper, van Veelen *et al.* (4) consider this question in a systematic way. Their answer is unexpected.

One of the most challenging scenarios in which to envisage the evolution of cooperation is where mutual cooperation pays well, but not cooperating (“defecting”) provides the higher immediate payoff to an individual, whether or not their partner cooperates. These inequalities help to define the Prisoner’s Dilemma, and any cooperation that evolves under these conditions must overcome defectors that exploit short-term gains.

Interest among biologists in the Prisoner’s Dilemma ballooned with the publication of a classic paper by Axelrod and Hamilton (5). The authors showed that although defectors would always rise to dominate a population in a one-off game, repeated interactions could facilitate cooperation by promoting the evolution of cooperative but conditional strategies (notably “tit-for-tat”). The role of cooperation in payoff-maximizing solutions to the iterated Prisoner’s Dilemma had long been appreciated by economists as an unaccredited (“folk”) theorem (6). However, Axelrod and Hamilton helped to show how natural

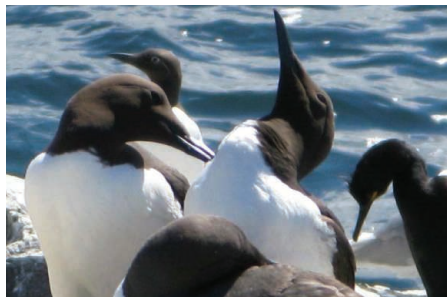
Cooperation now has many solutions, but recent work shows how two well-known mechanisms interact.

selection can influence which of many possible competitively successful outcomes of the repeated Prisoner’s Dilemma emerge. Moreover, they highlighted how the clustering of identical strategies in space (population structuring) could kickstart cooperation.

To evaluate how repeated interactions (which can facilitate conditional cooperation) and population structure (which can allow cooperative strategies to associate) combine to promote cooperation, van Veelen *et al.* started with the standard two-player iterated Prisoner’s Dilemma. The authors used a coefficient  $\delta$  to represent the probability that any given pair continues to play another round. At the same time, the authors represented the extent of population structuring in the system by using a coefficient  $\alpha$  to reflect an increase in the likelihood of interactions between identical strategies above the baseline based on random pairings.

The authors show by simulation and analytical approximation that as one increases  $\alpha$ , full cooperation always becomes more likely.

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However, previous research had already established that conditional cooperative strategies have an Achilles' heel ("weak stability") (7). They are invadable, through neutral drift, by unconditional cooperators that in turn pave the way for defectors, resulting in boom-and-bust cycles of cooperation and defection. Van Veelen *et al.* show that with increasing likelihood of continued interactions, the probability of this boom-bust scenario also increases, so that while the likelihood of a permanent defection equilibrium decreases, so does the likelihood of permanent cooperation. Thus, repeated interactions tend to facilitate cooperation in general, but require ever higher levels of population structuring ( $\alpha$ ) to promote permanent cooperation the higher the probability ( $\delta$ ) that individual pairs continue to interact.

Van Veelen *et al.* evaluate the nature of the interaction between two of the best-known routes to cooperation in the Prisoner's Dilemma. The folk theorem of economics emerges as a special case of their model, demonstrating that with no spatial structure cooperative solutions can evolve—albeit temporarily, so long as there is a sufficiently high continuation probability. However, Hamilton's rule (8) from evolutionary biology also emerges as a special case, such that even with zero continuation probability cooperation can still arise, so long as cooperators are sufficiently likely to interact with cooperators. The emergence of Hamilton's rule emphasizes the close link between population structure (represented by  $\alpha$ ) and kin selection, in which traits are favored because they disproportionately favor others carrying the same trait (9). Moreover, their results highlight the fundamental interrelationship among these seemingly different mechanisms, with conditional cooperation selected for much the same reason as it arises in spatially structured populations—cooperators helping cooperators (10).

What are behavioral biologists to make of their conclusions? All models are simplifications. Van Veelen *et al.*'s model assumes a fixed probability of interacting again, but individuals can often decide to terminate unsatisfactory interactions, and part-

**Pathways to cooperation.** Common murrelets (*Uria aalge*) regularly preen their mates, but they also form reciprocal preening associations with their close colony neighbors, highlighting two potential routes to cooperation: direct reciprocity and population structure. In a recent paper, van Veelen *et al.* (4) considered how these two routes to cooperation interact.

ner switching may be at least as important as partner fidelity in promoting cooperation (11). Likewise, the undermining of conditional cooperative strategies by neutral drift can be eradicated if conditional responses are continually favored by the need to recognize individuals who are unable to cooperate (12). The model accounts for conditional cooperation, but while reciprocity is readily demonstrated in experimental games involving humans, evidence for direct reciprocity in the nonhuman world is controversial (13). Van Veelen *et al.* state that human cooperation may be facilitated by "a strong dose of repetition and a pinch of population structure," but precisely the reverse—little repetition and a strong dose of population structure—provides the best opportunity for permanent cooperation. This leads us to wonder what type of cooperation would emerge if interaction rules  $\alpha$  and  $\delta$  were free to evolve under natural selection (14).

The problem of cooperation has now seen so many solutions that its existence can no longer be considered a puzzle. The existing literature can be classified coarsely as top down or bottom up, with the former approach discussing the problem of cooperation in

broad strokes and providing general solutions, and the latter approach taking observations of apparent altruism and providing specific explanations. At least some of these latter examples [e.g., (1)] may be understood on the basis of direct benefit rather than a Prisoner's Dilemma (15). Eventually, theory and observation will meet, and only then will we really know which general explanations apply to the world around us.

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10.1126/science.1226328

## CHEMISTRY

# Discriminating Chemical Bonds

Ruben Perez<sup>1,2</sup>

An atomic force microscope equipped with a functionalized tip can map out the electronic and structural properties of individual chemical bonds.

Recently developed operation modes for the atomic force microscope (AFM)—in particular, frequency modulation AFM (FM-AFM) (1)—have made it possible to image, manipulate (2), and chemically identify (3) both conducting and insulating surfaces (4) with atomic-scale resolution. On page 1326 of this issue, Gross *et al.* (5) push the limits of the imaging capabilities of AFM still further by using a functionalized tip—a metal tip with a carbon monoxide (CO) molecule at the apex—to map the subtle differences in charge density

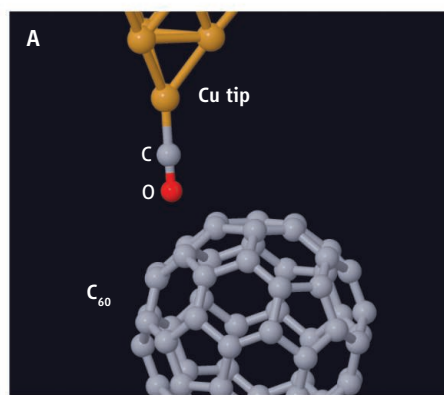
and bond length associated with nonequivalent C-C bonds in three complex molecular systems, and to correlate them with their bond order. The ability to determine fundamental properties of individual chemical bonds could affect many technologically relevant fields such as catalysis, photovoltaics, and molecular electronics.

The strength of the chemical bond between two atoms depends on their chemical environment. The C-C bond strength is progressively reduced in the series acetylene ( $\text{H}-\text{C}\equiv\text{C}-\text{H}$ ), ethylene ( $\text{H}_2-\text{C}=\text{C}-\text{H}_2$ ), and ethane ( $\text{H}_3-\text{C}-\text{C}-\text{H}_3$ ). This decreasing strength is related to the number of electrons shared by the C atoms (6, 4, and 2, respectively) to form what is referred to as a triple, double, or single C-C bond. Bond lengths correlate

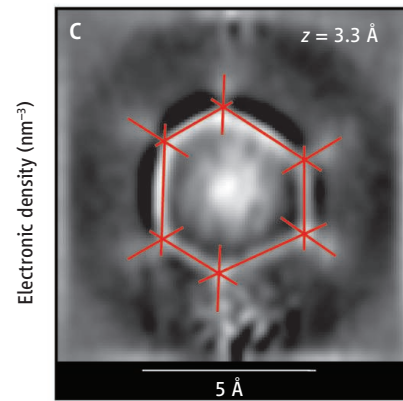
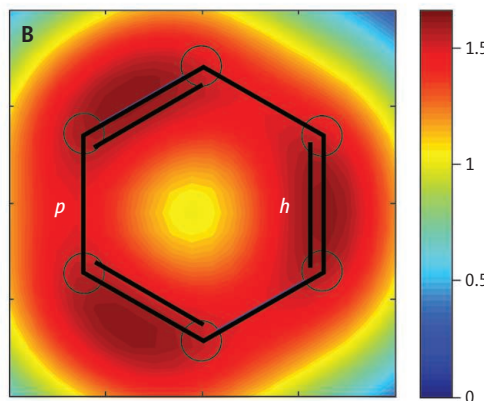
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**Forceful discrimination.** Gross *et al.* used AFM with a CO-functionalized tip (A) to map the subtle differences in charge density (B) and bond length (C) associated with nonequivalent C-C bonds in a fullerene ( $C_{60}$ ) molecule and to correlate them with their bond order.



with bond strength: A triple bond is shorter than a double bond, and this is shorter than a single bond. Characterizing the strength of the different bonds in a complex molecule is important in order to predict its geometry, stability, aromaticity, and reactivity. The Pauling bond order (6),  $P_b$ , captures that information in a single number. The bond order of the simplest conjugated molecule, benzene ( $C_6H_6$ ), is 0.5, reflecting the extra half bond provided by the six additional electrons that are equally shared among the six C-C single bonds defining the hexagonal ring. In more complex molecules, involving hexagons and pentagons,  $P_b$  can take any value between 0 (single bond) and 1 (double bond). In a fullerene ( $C_{60}$ ) molecule, the bonds fusing two hexagons ( $h$ ) are electron-rich compared to the bonds fusing a pentagon and a hexagon ( $p$ ), corresponding to  $P_h = 0.44$  and  $P_p = 0.28$ , and leading to differences in bond length of 5%.

Gross *et al.* show that those subtle differences in electronic charge distribution and length associated with the bond order can be directly measured on individual bonds of a fullerene molecule with the AFM. The key to this achievement is the use of a functionalized tip, in which a closed-shell CO molecule is attached, by the C atom, to the metal tip apex (see the figure). Density functional theory calculations show that the tip reactivity is crucial in determining the nature of the atomic contrast found in the AFM images (7, 8). With chemically inert tips, such as the CO-metal tip, the total tip-sample force is attractive mainly as a result of the long-range van der Waals contribution, but this interaction does not itself yield atomic contrast. Short-range chemical interactions are essentially repulsive (the Pauli repulsion between the overlapping electronic clouds),

and force maxima correspond to the positions with lower electronic density, like the hollow sites at the center of the carbon rings (8). FM-AFM measures the frequency shift, the change of the resonant frequency of the oscillating cantilever where the tip is mounted, due to the tip-sample interaction. Attractive (repulsive) forces produce a negative (positive) frequency shift. Gross *et al.* show that, for moderate tip-sample distances, the frequency shift is sensitive enough to map the differences in charge density associated with the different bond orders of individual bonds: It increases above the  $h$  bonds with respect to the  $p$  bonds, reflecting the stronger repulsion associated with the larger charge density in the  $h$  bond.

Those differences in frequency shift tend to blur when the tip is moved closer to the surface, but Gross *et al.* have found another way to discriminate between these bonds: The  $h$  bonds appear shorter relative to the  $p$  bonds. The real length difference, just 0.07 Å, would be at the limit of the AFM lateral resolution, but both bonds appear appreciably longer than they really are in the AFM images, resulting in a difference in apparent bond length 10 times larger. DFT calculations (5) prove that CO tips strike the perfect balance between being noninvasive and sensitive to the tip-sample interaction. When the tip-sample distance is reduced, the CO molecule can tilt in response to the larger repulsive interactions. This tip relaxation leads to an apparent expansion of the molecule in the image (roughly proportional to the local charge density) and the amplification of the subtle bond length differences. These capabilities have been confirmed in two large polycyclic aromatic hydrocarbons that contain bonds of several different bond orders, where AFM resolves differences in bond order down to 0.2 and distinguishes individual bonds that differ only by 0.03 Å in length.

The ability to map subtle differences in electronic density and length on individual bonds paves the way for a fundamen-

tal understanding of the charge redistribution processes that control electronic transport and chemical reactivity. Defects are crucial to tune the electronic properties of carbon-based materials like graphene, but they also affect the coupling with the local environment, which is critical to integrating them in tomorrow's electronic devices. AFM with CO tips offers the possibility of mapping the structural distortions and the subtle charge modulation predicted for single-atom vacancies and graphene nanoribbons. It has already been shown that a different type of force microscopy, Kelvin probe force microscopy, is able to control and measure the charge state of an individual atom (9) and to map changes in the local contact potential at submolecular resolution using a CO tip (10). Adding the new AFM capability to track small changes in the charge distribution around a bond should make it possible to use metal atoms attached to a molecule to add or remove charges and to identify the specific sites that would become active during a photochemical or electrochemical reaction. Future developments are not restricted to molecular systems. In the long term, one can envision the use of tips functionalized with tailored molecules exposing acidic or basic groups to identify and map the chemical reactivity of active centers in catalytic materials like transition metal and rare-earth oxides.

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10.1126/science.1227726

## RETROSPECTIVE

# Sir Bernard Lovell (1913–2012)

Albert A. Zijlstra and Richard J. Davis

Sir Alfred Charles Bernard Lovell, who died on 6 August at the age of 98, was a pioneer of radio astronomy. He is known as the founder of the Jodrell Bank Observatory and built its telescope, which bears his name. Fifty-five years after its inauguration, the Lovell telescope remains one of the largest steerable telescopes in the world.

Bernard Lovell was born in Oldham Common, near Bristol, UK, on 31 August 1913. He studied physics at the University of Bristol, where he earned his doctoral degree, and then moved to the University of Manchester in 1936 where he investigated cosmic rays under Professor Patrick Blackett. Apart from developing airborne radar systems for the military during World War II, he remained an academic in Manchester. He retired in 1981, but still regularly went to work until a few years ago. He received a knighthood in 1961, and was awarded the gold medal of the Royal Astronomical Society in 1981.

Patrick Blackett had a major influence on his life. He introduced Lovell to research in cosmic rays and, at the start of World War II, sent him to the radar group at Bawdsey Manor in 1939, a group under Blackett's committee. Lovell developed a radar system for "blind" targeting, which allowed night fighters to locate enemy aircraft, for example, and it became known as the H2S radar system. The war experience, when he was in his late 20s, would shape Lovell's life. After the war, again under Blackett's influence, Lovell used left-over radar equipment to study atmospheric radar echoes. This eventually led to the Lovell telescope, which incidentally incorporated parts of the gun racks of the battleships Royal Sovereign and Revenge.

Building the telescope left Lovell in major debt. This was not entirely his fault. The military requested that the dish surface of the telescope be upgraded so that it could operate at higher frequencies needed for radar detection of Soviet missiles. The extra weight necessitated expensive changes to the structure. But the Treasury noticed that two government departments were paying for the same project, contrary to the rules, and stopped the payment of the promised money. The modifi-



cations were put to good use when Sputnik 1 was launched on 4 October 1957, and the telescope could track the carrier rocket. This captivated the Americans, the press, and the public. During the late 1950s and 1960s, the telescope was often used to track both Russian and American satellites. It did this even for the Huygens probe landing on Saturn's largest moon, Titan. Deciding how much time to devote to such tracking or using the telescope for astronomical purposes was always a compromise. From 1962 to 1963, when the Ballistic Early Warning System at Fylingdales was being completed, only the Lovell telescope could give early warning if inter-continental ballistic missiles (ICBMs) were launched by the Russians. In one famous conversation (quoted from *Notes & Records of the Royal Society* 2008) as retold by Sir Bernard just weeks before his death, Lovell told the Chief of Air Staff that it would be possible to give notice of ICBMs lift offs, but nothing further could be done. The staff chief replied that in those 7 min he could save a million lives in London and the U.K.'s V-bomber force would be scrambled [airborne]. Through all the financial and design issues of the telescope, Lovell took personal responsibility for all matters relating to Jodrell Bank and the telescope. The massive debts eventually were paid through public and private donations.

Under Lovell's leadership, the Lovell telescope became an instrument for general radio astronomy, from flare stars to quasars. It was not the only such site in the United Kingdom; contemporaneous with, and also growing out of, radar development, Martin Ryle built up a radio observatory in Cambridge. But to the public, the Lovell telescope remained associated with the space race and is the main reason why U.K. radio

A physicist who helped to found radio astronomy and build one of the largest radio telescopes in the world.

astronomy is perceived as space science in a way that optical astronomy never has been. A newspaper referred to it as a "giant begging bowl held out to collect knowledge." A vibrant visitor center added to its public impact. Lovell remained director of the observatory until his retirement.

Sir Bernard had very diverse interests. Playing cricket was an important part of his life, and he captained the local team. When told that the Russians had launched a space probe and asked what he was going to do, he responded with "play cricket." He loved music, and until his 80s, played the organ in his church. He had a keen interest in science and religion and had considered a career in the church. Bernard Lovell was a generous person. But he is also remembered as a great storyteller. Stories abound about smuggling a Geiger counter into Ernest Rutherford's old laboratory, flying over the English Channel during D-Day, or being locked into the Cabinet office by Winston Churchill, who refused to let him out until he promised to get his radar system working within months. As a scientist he was uncompromising. He told a staff member not to spoil his first-rate data with second-rate theory. He was interested in recent scientific discoveries, and any visitors were likely to be quizzed on their work.

His legacy is without a doubt the Lovell telescope. It still inspires the public, and in some ways has become the poster child for the campaign to protect science budgets in the United Kingdom. There was a vehement public reaction to a threat to close it in 2008. It was chosen as the location for "Stargazing Live," a prime-time British Broadcasting Corporation program attracting 10 million viewers over three nights, for 2 years running. Its iconic status is due to a combination of visual impact, a populous environment, and its history as a U.K. contribution to the space race. The thriving visitor center keeps the vision of Sir Bernard alive, to bring the public in contact with live science and astronomers. E-MERLIN and the Square Kilometer Array Project provide links to the science of the future. Short-listed for World Heritage Site status, the Lovell telescope remains a living heritage of U.K. radio astronomy, to the credit of the scientific visionary who lived his life at the interface of science and society.

10.1126/science.1229080

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# Rinderpest Eradication: Appropriate Technology and Social Innovations

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Rinderpest is only the second infectious disease to have been globally eradicated. In the final stages of eradication, the virus was entrenched in pastoral areas of the Greater Horn of Africa, a region with weak governance, poor security, and little infrastructure that presented profound challenges to conventional control methods. Although the eradication process was a development activity rather than scientific research, its success owed much to several seminal research efforts in vaccine development and epidemiology and showed what scientific decision-making and management could accomplish with limited resources. The keys to success were the development of a thermostable vaccine and the application of participatory epidemiological techniques that allowed veterinary personnel to interact at a grassroots level with cattle herders to more effectively target control measures.

Rinderpest was declared eradicated by the World Organization for Animal Health in May 2011 (1), the second disease ever to be globally eradicated. The disease affected cattle and water buffalo with severe consequences for household livelihoods, and its long history in Europe and Asia was closely intertwined with war, drought, and famine. For millennia it was considered to be the animal disease with the greatest impact on human well-being (2, 3).

Rinderpest is an RNA virus and a member of the genus morbillivirus, which, as the name suggests, includes other notorious pathogens such as peste des petits ruminants (PPR), measles, and canine distemper. The classic presentation of rinderpest was a fulminating diarrhea leading to dehydration and death, often wiping out a family's cattle in a matter of days. There is no treatment for rinderpest.

A series of control programs in Europe from the 17th century, often credited as the first attempts at organized disease control (4), sought to contain and eliminate rinderpest (5, 6). These efforts were associated with many technical and organizational innovations ranging from the founding of the first veterinary school in Lyon, France, in 1761 to the first use of the rectal thermometer in 1866 (7). Rinderpest's relatively recent arrival

in Africa via the port of Massawa, Eritrea, in the 1880s resulted in 90% mortality in cattle and cloven-hoofed ungulates (artiodactyls) as it swept southward to the Cape, causing widespread famine and ecological change (8) (Fig. 1). These events directly led to the founding of the Office International des Epizooties (OIE) in 1924 (9) and the African Union Interafrican Bureau for Animal Resources (AU-IBAR) in 1951.

Early attempts to control rinderpest in Africa led to technical innovations such as the Koch's serum/virus method of immunization in 1897 and Edwards' goat-adapted vaccine in 1941 (7). The first tissue-culture-produced rinderpest vaccine was developed in 1960 by Plowright (10), and its availability inspired Joint Project 15 (JP15), a coordinated effort to eradicate rinderpest from Africa based on mass vaccination. By the 1970s, the range of rinderpest in Africa was reduced to two areas, the Niger Inland Delta in Mali in western Africa and southern Sudan in eastern Africa. With the decline of direct disease impact, the sense of urgency was lost, and the completion of eradication was left to national governments to handle individually through annual vaccination of calves. In the ensuing decade, rinderpest resurged across Africa, again causing up to 90% mortality in its wake. In the late 1980s, a second coordinated effort to eradicate rinderpest, the Pan-African Rinderpest Campaign (PARC), was launched. Initially, as with JP15, mass vaccination targeting entire national populations carried out by teams of government veterinary service personnel was the main approach employed. By the 1990s, rinderpest was largely, but not entirely, confined to remote endemic areas of eastern Africa such as southern Sudan, the Afar region of Ethiopia, the Karamojong region of Uganda, and the Somali rangelands, where insecurity, chronic conflict, and weak governance created challenging environments for vaccine delivery. The eradication effort was drifting toward indefinite disease

containment of remote endemic areas (11), with donor fatigue looming on the horizon.

Here, we focus on the evolution of vaccination and surveillance approaches in Africa that enabled the eradication of rinderpest on a tight budget. The approach that ultimately led to success was pragmatic, with surveillance activities mainly identifying infected areas through detection and confirmation of a handful of index cases. Success of interventions was evaluated on the basis of their ability to cause the disappearance of disease. This approach could equally be applied to livestock disease control if a vaccine is available, transmission rates are not overwhelming, and where community stakeholders want eradication and will participate in achieving it and thereby facilitate access to remote areas. We explore the potential of applying these principles to other livestock diseases in less-developed countries.

## Development of the Thermostable Rinderpest Vaccine

The early rinderpest vaccines were superseded by Plowright's tissue-culture-produced vaccine. This vaccine was successful because a single tissue culture infectious dose conferred lifelong protective immunity to all strains of the virus; the vaccine virus had no reported adverse reactions, and it was inexpensive and relatively easy to produce (12). However, its major shortcoming was that it required strict, expensive, and logistically difficult refrigeration (known as a "cold chain"). Hence, in 1981, the development of a thermostable rinderpest vaccine was identified as a research priority (13).

The thermostability of the Plowright vaccine was enhanced by improved production and lyophilization techniques (14) and adapted to the Vero cell line to further simplify production. Modified lyophilization resulted in a vaccine with a shelf life of more than 8 months at 37°C, which was sufficient to recommend the vaccine for use in the field for up to 30 days without a cold chain. Registration of the thermostable product, Thermovax, was based on an existing vaccine virus in wide use, and the new vaccine was in commercial-scale production and available for purchase by 1992, just 4 years from the start of the research (14, 15).

## Technical Innovation as a Driver of Institutional Change

Now a vaccine was available that could be delivered on foot, by animal transport, or by bicycle and sent to remote areas. Vaccination with thermostable vaccine in marginalized communities became a cornerstone of the end-game eradication strategy (16, 17) and required a rethinking of service delivery that allowed new partnerships, such as community animal health programs (18), to achieve full vaccination coverage.

Institutional change was accomplished by public-private-community partnerships in which

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veterinarians delivered services through community members using approaches adapted to local institutions. The local intermediaries, called community-based animal health workers (CAHWs), were willing to travel on foot and able to work in remote areas (Fig. 2). They were trained to vaccinate livestock (19), and thus more remote communities were able to implement vaccination campaigns. Not surprisingly, some members of both official and private veterinary services saw this new paradigm as a threat to their livelihoods and opposed the implementation of such field programs. Incentives that were mutually favorable to the communities and professionals had to be carefully crafted to allow communities to vaccinate with the shared oversight of the veterinarians and community elders (19). In this way, rinderpest vaccination was integrated into broad community-based animal health programs that addressed a range of animal health priorities identified by local communities (20, 21). Local knowledge of the sizes of cattle herds, their location, seasonal movement patterns, and the optimum time for vaccination was essential for planning and extending effective rinderpest vaccination coverage to areas not covered by public programs. Because the CAHWs had participated in planning vaccination, and the thermostable vaccine allowed flexibility, the CAHWs could adjust their work to allow for changes in cattle movement patterns or unexpected events, in sharp contrast to inflexible vaccination campaigns that resulted in poor vaccination coverage. Community-based vaccination programs thus achieved herd immunity levels greater than 80% and were at least as effective as the best public veterinary service programs in Africa conducted in more accessible areas (19, 22, 23).

### Participatory Approaches to Gathering Epidemiological Intelligence

Before the PARC, surveys of animal health knowledge systems of pastoral communities uncovered a rich source of information for planning animal health activities (24). Participatory rural appraisal evolved into a more comprehensive and effective tool kit of methods for understanding local knowledge that could be integrated into the design of the community programs. The advent of community-based rinderpest vaccination activities in PARC brought mainstream animal health personnel into direct contact with community health knowledge and methods for its study. The outcome was a real-time field intelligence approach to the collection of epidemiological information

to guide decision-making on rinderpest control options.

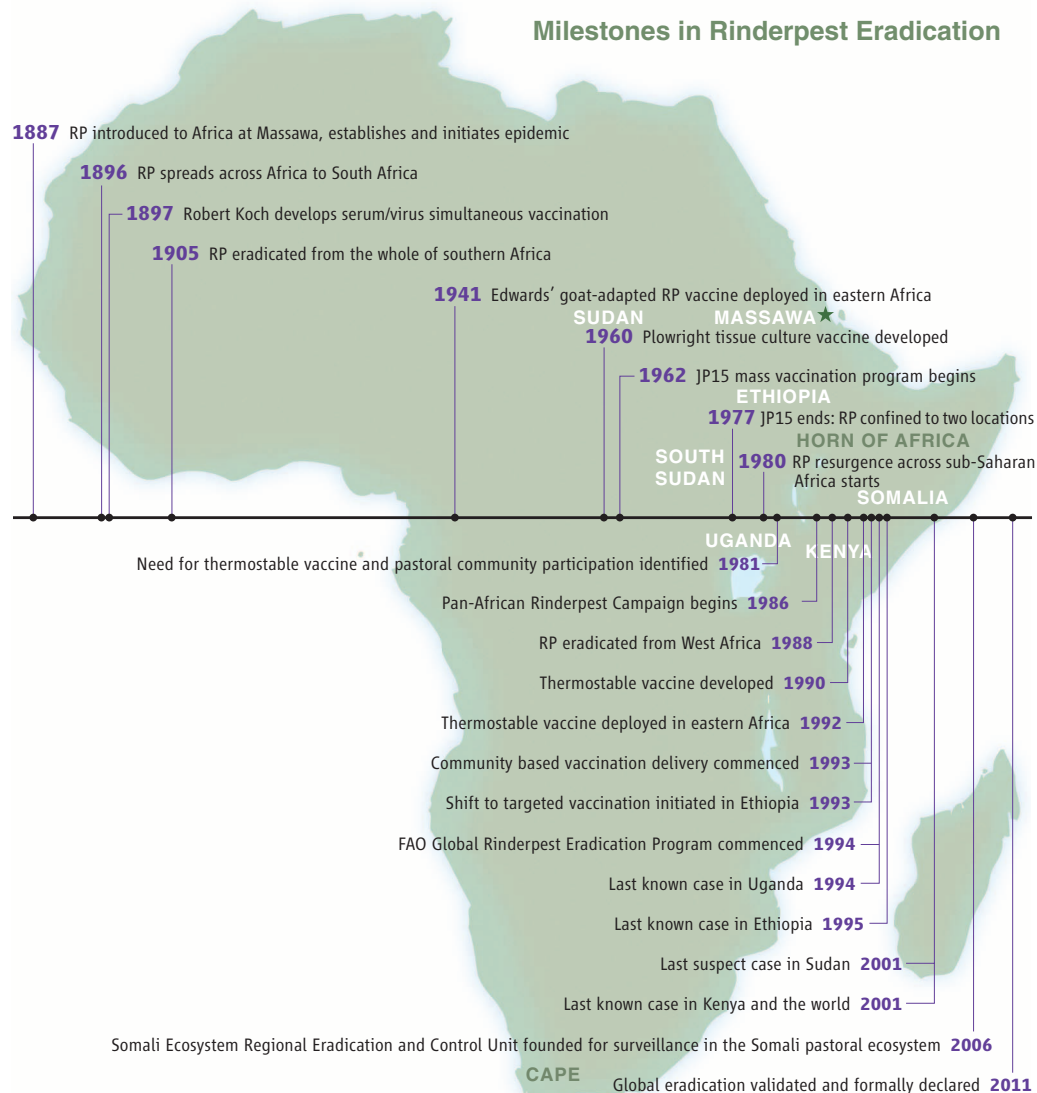
Pastoral communities have a detailed understanding of the presentation, distribution, epidemiology, and history of key livestock diseases in their area. (25, 26). Livestock owners provided information that led to the identification of several of the final outbreaks of rinderpest where conventional surveillance activities had failed to disclose disease (27). In the later stages of disease eradication, participatory disease surveillance was an important tool in the recognition of freedom from rinderpest (28). The World Organization for Animal Health guidelines for recognition of disease freedom focused on randomized serosurveillance as a final objective check to validate eradication, but due to its high cost, it was usually only implemented after there was a consensus among program advisors that the disease had been eradicated. To the authors' knowledge, serosurveillance never identified any occult circulation of

virus, thus validating pastoralists' participation in the eradication strategy.

This mainstream recognition of livestock owner knowledge and the development of participatory epidemiology and surveillance have now been extended to the control of other diseases, such as PPR (29), Rift Valley fever, highly pathogenic avian influenza (30, 31), and foot-and-mouth disease (FMD) (32).

### Epidemiological Targeting

Throughout the 1980s and into the 1990s, rinderpest programs used annual, pulsed, mass vaccination programs, where the goal was to cover entire national populations and surveillance was based on passive disease-reporting systems. Rather than cessation of virus circulation, mass vaccination programs were judged on the numbers of vaccinations performed relative to overall national populations, which were often inaccurately defined. Populations that were difficult to access



**Fig. 1.** A timeline of major events in the history of rinderpest in Africa from its introduction in 1887, in military cattle brought to Eritrea to feed troops, to the declaration of rinderpest's eradication in 2011. RP, rinderpest.

were repeatedly overlooked for decades, resulting in highly variable herd immunity and reservoirs of virus persistence.

Mathematical modeling of measles has shown that maximal vaccination impact is achieved by focusing resources on those populations with the highest transmission rates (33) and with sizes larger than the community size required for sustained transmission (34). Building on this work, stochastic state transition models explored the transmission dynamics of the two lineages of rinderpest existing in Africa. This allowed estimation of the vaccine coverage levels needed to interrupt transmission and the minimum population size required to sustain transmission, and predictions of the impact of focused vaccination at different levels of coverage (35). The analysis made use of serological data from selected endemic communities where vaccination had not been practiced. The estimates of the mean basic reproductive number ( $R_0$ ), the number of new cases resulting from one infected animal introduced into a fully susceptible population, were 4.6 for lineage 1 (Sudan) and 1.5 for lineage 2 (Somali), which implied that the herd immunity thresholds for the interruption of transmission were 77 and 33%, respectively. The modeling indicated that the community size required for sustained transmission was in the order of 200,000 head for both lineages. This information reinforced the view that seeking greater than 80% immunity was adequate for remote Sudanese livestock in excess of 200,000 head. Managers were skeptical that a 33% vaccination rate could interrupt transmission of rinderpest in the Somali ecosystem, but rinderpest was conclusively eradicated from the Somali ecosystem with cattle herd immunity levels that probably never exceeded 50%, despite best efforts to achieve 80%.

Because available serologic tests could not differentiate antibodies induced by vaccination from those resulting from natural infection, serological approaches to the estimation of the effective reproductive number, or  $R_e$  (the reproductive number in populations where mitigation measures have changed susceptibility or effective contact rates), were of little use to monitor the effectiveness of vaccination strategies. Likewise, it was not possible to use analysis of individual outbreaks for the estimation of  $R_e$ , because rinderpest outbreaks developed rapidly in remote and insecure areas in mobile cattle populations. Rather, local intelligence of rinderpest infections gathered through participatory surveillance was the most successful approach to assessing the impact of vaccination methods and monitoring strategic progress toward eradication.

Livestock contact patterns are largely the result of human interactions. The use of participatory epidemiology and community animal health services heightened the awareness of how cultural differences and social relationships among pastoralists contributed to the patterns of rinderpest transmission (35) and influenced the transmission links between populations. However, a

concerted effort using both field and modeling results was often required to convince decision-makers to adopt risk-based approaches (35). Effective coordination mechanisms—such as the Global Rinderpest Eradication Program at the United Nations Food and Agriculture Organization (FAO) and the Somali Ecosystem Rinderpest Eradication and Coordination Unit at the AU-IBAR—facilitated the uptake of targeted approaches. Once this focused approach was adopted in countries such as Ethiopia, Uganda, and Sudan, no infections were detected after 2 years.

Ethiopia provided a textbook example of the enhanced impact of targeted vaccination. From April 1989 to July 1990, at the peak of mass vaccination activity, 21.4 million vaccinations were performed. This represented up to 95% coverage in accessible areas but only 69% coverage nationally (36). Remote areas were not vaccinated year after year and acted as endemic reservoirs of infection where virus continually circulated. In 1993, based on disease intelligence, the country was divided epidemiologically into free, epidemic, or endemic zones, and vaccination was limited to endemic zones and some surrounding areas at high risk. The annual national vaccination target was reduced to less than 3 million, but these were among the most difficult cattle to reach in the country. Community animal health workers played a major role in reaching these remote cattle and eradicating rinderpest from this and other challenging areas of East Africa (Fig. 2). The result of the shift in strategic focus was that after decades of struggle to control rinderpest, the disease was not detected in Ethiopia after October 1995.

#### Comparisons Across Disease Eradication Programs

The rinderpest eradication effort succeeded even though the classic animal disease control options of movement control and culling of infected animals were not available for economic and social reasons. The core strategy that was finally successful identified infected communities and then interrupted transmission in those communities with thermostable vaccine delivered by local participants.

Pathogens with a low  $R_0$  are generally easier to control because each case results in only a limited number of secondary cases. A low  $R_0$  is why severe acute respiratory syndrome was much easier to contain than measles or FMD outbreaks. Rinderpest had an  $R_0$  of 4.6 for lineage 1, which meant that even virulent strains only required 77% herd immunity for elimination to occur and helped to explain why targeted vaccination alone

was so effective. Epidemiological indicators other than  $R_0$  that should be considered in assessing the difficulty associated with controlling a disease and selecting control methods are the length of the generation interval of the infection between cases in chains of transmission and the life expectancy of hosts. The average life expectancy of a cow in Africa is on the order of 5 years; by adopting a series of annual vaccination cycles, this life span allowed the rinderpest program to build herd immunity. In contrast, although highly pathogenic avian influenza has a low  $R_0$ , high poultry population turnover and the short duration of vaccine-induced



**Fig. 2.** Community animal health workers equipped with thermostable vaccine eradicated rinderpest from the chronically insecure regions of East Africa. A Karamojong community animal health worker, Tom Olaka, is shown vaccinating his community's cattle with thermostable rinderpest vaccine in 1994. Olaka also identified and reported the last outbreak of rinderpest from this insecure area and enabled the completion of the eradication of rinderpest from Uganda. [Photo by Christine Jost]

immunity makes it impossible to build adequate flock immunity in free-ranging village poultry.

An important aspect of the rinderpest story is that social change altered the efficacy of control options over time. The mass vaccination approach that worked fairly well across Africa during the time of JP15 did not work in those communities by chronic conflict or failed infrastructure. Similarly, contagious bovine pleuropneumonia (CBPP) was eliminated from large parts of Africa in the colonial era using mass vaccination with a moderately effective vaccine and draconian movement control. With modern pluralistic governance, strict movement control is no longer feasible and CBPP has reentered many areas.

As a result of the rinderpest success, the international animal health community has become interested in adopting coordinated approaches to



progressive control of disease in small ruminants. Small ruminants have a life expectancy on the order of 1 year, are traded heavily, and constitute an important disease transmission challenge. PPR, caused by a virus related to rinderpest, shares many attributes that make it a good prospect for eradication. As a disease of sheep and goats, PPR has a direct impact on the food security and well-being of the most impoverished communities. Against this backdrop, the Executive Council of the African Union and the participants of the FAO Global Rinderpest Eradication Symposium have urged that appropriate programs for the progressive control of PPR be undertaken (37). Strategies have been put forward to coordinate the current investment in PPR control as a progressive control program with the ultimate objective of eradication (38, 39). The development of more effective vaccination models that address the challenges of immunizing mobile populations of rapidly reproducing small ruminants is a major research objective. This time around, the research must integrate institutional and technical innovations from the start.

Similar considerations apply to FMD virus, for which the goal of elimination through a strategy of progressive control is increasingly discussed. The loss of production and export markets resulting from the presence of FMD make this disease a priority for commercially oriented livestock producers and national economies. A conservative estimate of 4.6 was given for  $R_0$  during the early stages of the FMD outbreak in the United Kingdom in 2001 (40), and in certain circumstances, such as intensive dairy farming in the Kingdom of Saudi Arabia,  $R_0$  might even exceed 70 (41), implying herd immunity thresholds of 98% and 99%, respectively. In practice, such herd immunity is not achievable. On the other hand, although FMD is a concern to almost all livestock farmers, many traditional producers find that they can cope with periodic FMD-induced production loss. Pastoralists and small-scale farmers place a much higher priority on the risk of diseases that cause catastrophic losses and failure of household livelihoods. Thus, there are serious issues of incentives for participation in FMD elimination among key livestock-keeping stakeholder groups who prioritize the well-being of their families over national economies.

In some ways, the rinderpest approach—searching for infected populations, followed by the application of intensive vaccination—was similar to that used for smallpox, but in the latter case the search extended to identifying and isolating infected individuals. The necessary distinction in value between human lives and that of their livestock shapes the control options available to the medical and veterinary professions and is often the elephant in the room in discussions on “one health” approaches based on integration of human, animal, and ecosystem health activities.

### Lessons for the Future

The primary lesson was that the vision of a rinderpest-free world was both tangible and

broadly valued by stakeholders. This easily understood goal stimulated the imagination and induced stakeholders to risk change in fundamental areas of animal health practice and human behavior.

The second lesson was that, despite the advent of the thermostable vaccine, this new technology alone could not solve institutional issues. The reluctance of researchers to champion the process of social change accompanying the deployment of new technologies might in part explain why many products of research fail to have impact. The technical research to develop a thermostable rinderpest vaccine required 2 years to complete, but the social innovation to capture the benefit required more than a decade. Ultimately, a clear institutional understanding that recognized the legitimate needs of each stakeholder group and the power relationships between groups was needed before the thermostable vaccine could achieve its full potential. An institutional analysis at the outset might have accelerated change.

The third lesson concerned the optimal gathering and use of information in decision-making. Resources for animal health surveillance in the developing world are limited. Conventional surveillance data for rinderpest were insufficient to reliably indicate the presence of disease. The use of pastoralists' knowledge in surveillance was found to be critical for targeting eradication efforts. Ideally, a serological test to distinguish between vaccinal and natural immunity would have made epidemiological studies more robust but was not at all a prerequisite for success.

Internationally, the call is out to apply the lessons of rinderpest eradication to the notorious morbillivirus PPR as the distribution and impact of this infection has extended to most of Africa and across Asia to China.

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**Acknowledgments:** The eradication of rinderpest was a global undertaking that received support from a wide range of national governments and international agencies. Principal support for the later stages of eradication was provided by the European Union. The U.S. Agency for International Development supported research leading to the thermostable rinderpest vaccine. Preparation of this manuscript was supported by the International Livestock Research Institute and Tufts Cummings School of Veterinary Medicine.

10.1126/science.1223805

# Adaptive Prolonged Postreproductive Life Span in Killer Whales

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The evolution of a prolonged postreproductive life span has attracted considerable interdisciplinary attention, primarily because of the long postmenopausal life span seen in humans (1). Two mechanisms have been proposed to underpin prolonged postreproductive life span: (i) an epiphenomenon of increased longevity, in which evolutionary benefits accrue only during the reproductive phase with no additional fitness benefits after the last reproductive event, and (ii) an evolved adaptation in which postreproductive life span increases the survival of an individual's genes, increasing its inclusive fitness. There is mounting evidence that postreproductive human females increase the reproductive success and survival of their offspring (2, 3). Although helping in some postreproductive female cetaceans (4) suggests an adaptive benefit, there has been no evidence that a similar phenomenon occurs in nonhuman animals.

With multigenerational demographic records based on photographic censuses (1974 to 2010) of the Southern and Northern resident killer whale (*Orcinus orca*) populations in coastal waters off Washington state, USA, and British Columbia, Canada [see (5) for details], we used a Cox proportional hazards model (6) to examine the consequences of a mother's death on offspring survival.

This unique data set consisted of 589 individually identifiable animals, of which 297 died during the study period (6).

Resident killer whales have the longest postreproductive life span of all nonhuman animals: Females stop reproducing in their 30s to 40s but can survive into their 90s (5). Because neither sex disperses from the maternal group (7), theory based on kinship dynamics (4) predicts that female's relatedness to her group increases with age and that old mothers maximize their fitness by ensuring their offspring's survival and reproductive success. There is an asymmetry, however, in the benefits of helping sons and daughters. Mating occurs outside of the matriline; thus, a son's offspring are raised by another group (where any rearing costs are incurred), whereas a daughter's offspring are raised within the group, increasing within-group competition (4). Old mothers can therefore maximize inclusive fitness benefits by directing care toward sons (4).

Postreproductive mothers are known to have little effect on their daughter's reproductive success in resident killer whales (8). However, we show that both postreproductive and reproductive females increase their own offspring's survival, particularly older male offspring (Fig. 1 and table S1). For male offspring  $\leq 30$  years old, there is a 3.1-

fold increase in mortality risk in the year after their mother's death (Fig. 1). For males  $>30$ , this risk increases to 8.3-fold (Fig. 1). In contrast, female offspring  $\leq 30$  show no increase in mortality risk, whereas those  $>30$  show some increase in risk (2.7-fold) in the year after their mother's death (Fig. 1). Importantly, the magnitude of this effect does not differ between reproductive and postreproductive females (6). Indeed, for offspring  $>30$ , the death of a postreproductive mother increases mortality risk 13.9-fold in sons and 5.4-fold in daughters in the year after their mother's death.

Our results demonstrate an adaptive benefit to a prolonged postreproductive life span in killer whales. Because reproductive success increases with age in male killer whales (9), increasing the survival of older male offspring will maximize inclusive fitness (4). Resident killer whales are unusual in that mothers maintain strong social relations with their adult sons throughout their lives (7). Mothers may increase the survival of their adult sons in a number of ways, including assisting in foraging and providing support during agonistic encounters (10). Crucially, the fact that mothers increase the survival of male offspring, which do not terminate reproduction early (9), may explain why killer whales have evolved the longest postreproductive life span of any nonhuman animal.

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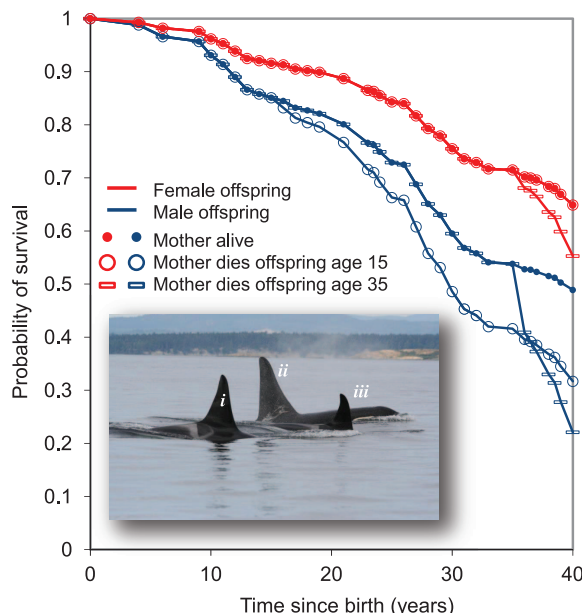
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**Acknowledgments:** We thank our colleagues for their important roles in data collection over the past 35 years, particularly M. Bigg, D. Ellifrit, G. Ellis, E. Heydenrich, and A. van Ginneken and the Biotechnology and Biological Sciences Research Council and the Leverhulme Trust for funding. Data are available in the supplementary materials.

## Supplementary Materials

www.sciencemag.org/cgi/content/full/337/6100/1313/DC1  
Materials and Methods

2 May 2012; accepted 27 July 2012  
10.1126/science.1224198



**Fig. 1.** Survival curves derived from a Cox proportional hazards model (6) for male and female offspring experiencing their mother's death at different ages. (Inset) Adult sons (i and ii) traveling with their postreproductive mother (iii).

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# Octet-Line Node Structure of Superconducting Order Parameter in $\text{KFe}_2\text{As}_2$

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In iron-pnictide superconductivity, the interband interaction between the hole and electron Fermi surfaces (FSs) is believed to play an important role. However,  $\text{KFe}_2\text{As}_2$  has three zone-centered hole FSs and no electron FS but still exhibits superconductivity. Our ultrahigh-resolution laser angle-resolved photoemission spectroscopy unveils that  $\text{KFe}_2\text{As}_2$  is a nodal *s*-wave superconductor with highly unusual FS-selective multi-gap structure: a nodeless gap on the inner FS, an unconventional gap with “octet-line nodes” on the middle FS, and an almost-zero gap on the outer FS. This gap structure may arise from the frustration between competing pairing interactions on the hole FSs causing the eightfold sign reversal. Our results suggest that the  $A_{1g}$  superconducting symmetry is universal in iron-pnictides, in spite of the variety of gap functions.

**K** $\text{Fe}_2\text{As}_2$  is the end member of the hole-doped  $(\text{Ba}_{1-x}\text{K}_x)\text{Fe}_2\text{As}_2$  (BaK-122) series of pnictide superconductors. The optimally doped ( $x \sim 0.4$ ) member of the series possesses the representative features of iron-based superconductors (1): an electronic structure that is derived from multiple Fe-3d orbitals and con-

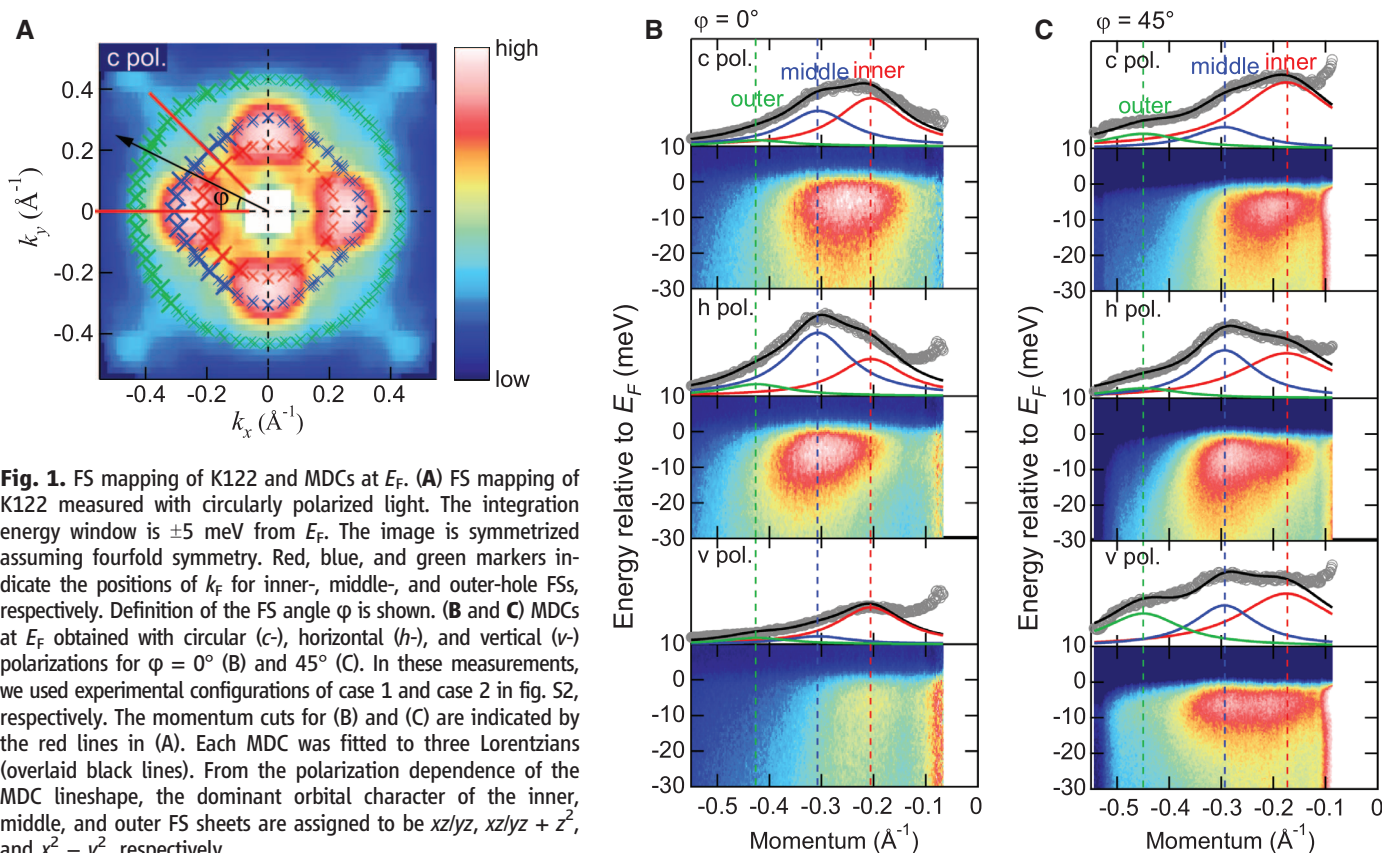
sists of hole Fermi-surface (FS) sheets around the zone center ( $\Gamma$  point), electron sheets around the zone corner ( $X$  point), and a fully gapped superconducting state (2, 3). In  $\text{KFe}_2\text{As}_2$  ( $x = 1$ , K122), for which there is experimental evidence (4–6) of gap nodes, the extreme hole doping changes the electron sheets to the clover-like hole pockets, which

makes this material distinctly different from other iron-based systems, including the possible nodal superconductors  $\text{LaFePO}$  (7) and  $\text{BaFe}_2(\text{As,P})_2$  (8, 9). This property of K122 has led to a recent theoretical suggestion of *d*-wave superconductivity with gap nodes in the all-zone-centered hole bands (10, 11), which would imply a phase transition featuring a change in the superconducting gap symmetry from *s*- to *d*-wave as a function of doping  $x$ . In support of this picture, recent thermal conductivity measurements (12) suggest a possible

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*d*-wave gap symmetry in K122. It is therefore important to determine the gap symmetry and positions of the nodes in the Brillouin zone of K122.

Recently, we have developed a laser-excited angle-resolved photoemission spectroscopy (laser ARPES) apparatus that achieves a maximum energy resolution of 70  $\mu\text{eV}$  and lowest cooling temperature of 1.5 K (13). This high-energy resolution indicates very high stability of the Fermi level ( $E_F$ ) position, enabling a direct measurement of the superconducting (SC) gap of K122, which has a critical temperature ( $T_c$ ) as low as 3.4 K (14).

We first resolve and analyze the FSs of K122 around the Brillouin-zone (BZ) center. The FS map of K122 is shown in Fig. 1A, with an energy resolution of 4 meV with circularly polarized light, and the momentum distribution curves (MDCs) at  $E_F$  are shown in Fig. 1, B and C, measured with the circularly (*c*), horizontally (*h*), and vertically (*v*) polarized light (definition of polarization is provided in fig. S2) for the cuts along the azimuth angles  $0^\circ$  and  $45^\circ$ , respectively (Fig. 1A). Each MDC can be fitted to three Lorentzians, resolving three-hole FSs around the BZ center as predicted with band-structure calculations (15, 16). The Fermi momentum ( $k_F$ ) obtained (symbols) from the fits are overlaid on the FS map in Fig. 1A (the determination of the  $k_F$  positions of the other cuts are provided in fig. S3). The MDC line shapes depend on the polarization of the incident laser because of the parity selection rules, and accordingly, we can determine the dominant orbital

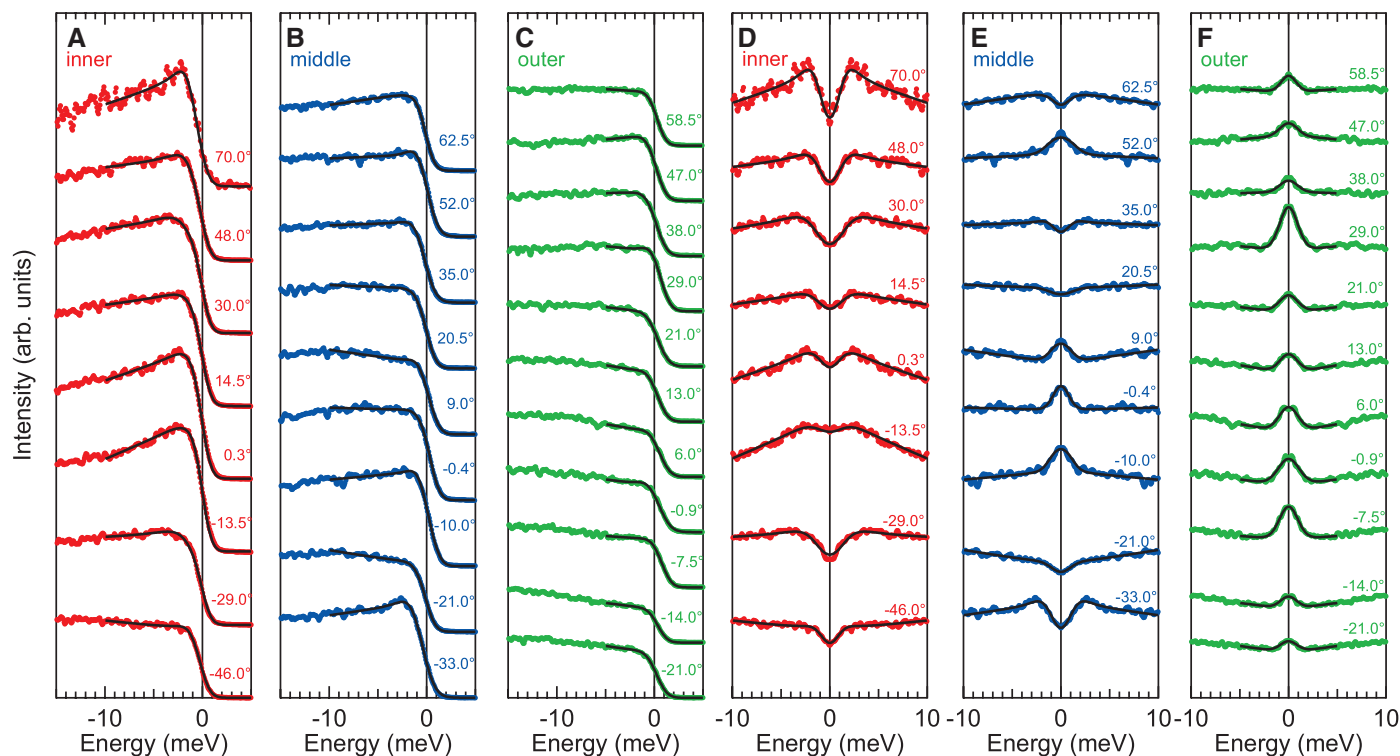
character of the inner-, middle-, and outer-FS sheets to be  $xz/yz$ ,  $xz/yz + z^2$ , and  $x^2 - y^2$ , respectively (13).

The energy distribution curves (EDCs) at  $k_F$  of the inner, middle, and outer FSs measured at 2.0 K (below  $T_c$ ) are shown in Fig. 2, A to C. Each EDC at  $k_F$  is identified with a FS angle  $\phi$  (Fig. 1A). The  $k_F$  positions were obtained from MDCs measured with a lower resolution of 4 meV and confirmed by the quasiparticle behavior seen in the EDCs measured at 2.0 K, below  $T_c$  (EDCs of representative cuts are provided in fig. S6). The EDCs shown in Fig. 2, A to C, were symmetrized with respect to  $E_F$ , and the results are shown in Fig. 2, D to F, respectively. The valley structures at  $E_F$  observed in the symmetrized EDCs of the inner FS (Fig. 2D) indicate the opening of a SC gap for all FS angles with some anisotropy in the gap size. For the middle FS, the symmetrized EDCs in Fig. 2E show peaks or valleys at  $E_F$  as a function of FS angle, indicating that the SC gap is more anisotropic and is almost closed around  $\phi = 0^\circ$  (17). For the outer FS, the symmetrized EDCs show a peak structure for all angles in Fig. 2F, indicating that the size of the SC gap seems to be almost zero for all FS angles. Thus, there is a clear FS sheet dependence in the SC-gap size of K122, which is in strong contrast to the optimally doped BaK-122 (18) but is consistent with the evolution of the gaps as a function of K doping (19). In order to quantify the SC-gap size, we have fitted the EDCs to the Dynes' function (20).

Although this function is appropriate for the density of states, we have also confirmed that all the EDCs can be fitted to the Bardeen-Cooper-Schrieffer (BCS) spectral function used in (18), and they give almost the same SC-gap sizes [a comparison of the Dynes' and spectral function fits and the reason why we chose the Dynes' function is given in (13)]. We were able to fit all of the EDCs to calculated spectra (Fig. 2, solid lines) (21).

To confirm whether or not the gap is really closed around  $\phi = 0^\circ$  of the middle FS, we performed detailed measurements in this region with increased accuracy of the  $E_F$  position. We show the EDCs and symmetrized EDCs in Fig. 3, A and B, respectively, for  $\phi = 8.9^\circ$ ,  $4.0^\circ$ , and  $-0.5^\circ$ ; the solid lines indicate the fits to the Dynes' function. The spectra at  $\phi = 8.9^\circ$  and  $-0.5^\circ$  acquire small but finite SC gaps, whereas the gap is closed around  $\phi = 4.0^\circ$ . Furthermore, we have measured the temperature dependence of the spectra. The EDCs above and below  $T_c$  close to the node ( $\phi = 5.0^\circ$ ) and off the node ( $\phi = 22.7^\circ$ ) are shown in Fig. 3, C and D, respectively. The leading edge does not shift for the EDCs near the node, but a finite shift can be observed for the EDCs off the node. This indicates that the nodal points exist around  $\phi = 5.0^\circ$ .

We plot the SC-gap sizes derived from the Dynes' function fits as a function of FS angle in Fig. 4A. The solid circles are derived from the EDCs shown in Fig. 2, and the open circles are plotted by symmetrizing the data, taking into



**Fig. 2.** EDCs and symmetrized EDCs at  $k_F$ . (A to C) EDCs at  $k_F$  of (A) inner, (B) middle, and (C) outer FSs, respectively, taken at 2.0 K ( $<T_c = 3.4$  K) for various FS angles as shown in each panel. The integration angle window is  $\pm 0.5^\circ$  ( $\sim \pm 0.0075 \text{ \AA}^{-1}$ ) from  $k_F$ . (D to F) Symmetrized EDCs of (D) inner, (E)

middle, and (F) outer FSs, respectively. By symmetrization, the temperature dependence of the FD function can be canceled out so that the symmetrized EDCs approximately reflect the spectral functions around  $E_F$ . The fits to the Dynes' function are indicated by the solid lines.

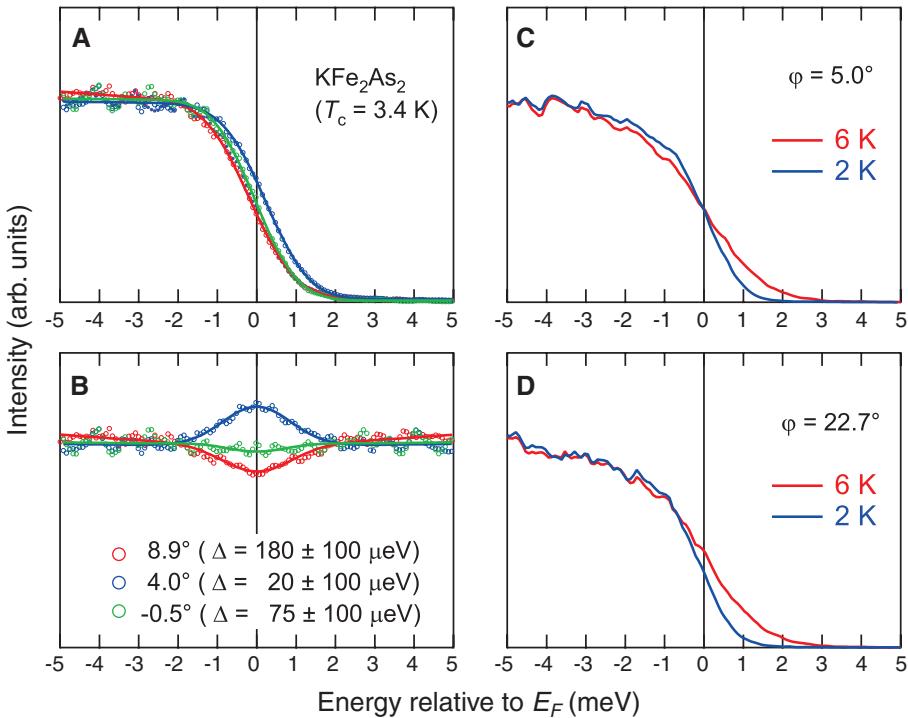
account the tetragonal crystal symmetry. In addition, the results of several high-resolution measurements around  $\varphi \sim 0^\circ$  for the inner and middle FSs are also plotted with open rectangles, triangles, and diamonds. In the inset, the SC gaps around  $\varphi \sim 0^\circ$  of the middle FS are plotted on an enlarged scale. First of all, a fully gapped structure without nodes on the inner FS is consistent with the *s*-wave symmetry and excludes the *d*-wave symmetry with nodes as suggested theoretically (10, 11) and experimentally (12). In addition, the SC gap structure on the inner and middle FSs shows strong anisotropy, whereas that on the outer FS is vanishingly small. To obtain insight into the angle dependence of these SC gap functions, we have tried to fit them with two lowest harmonics under the fourfold tetragonal symmetry

$$\Delta(\varphi) = |\Delta_0[1 + A \cos(4\varphi) + B \cos(8\varphi)]| \quad (1)$$

Such  $\cos(4\varphi)$  term has been considered in some theoretical works (22, 23). In our case, the inclusion of the higher-order  $\cos(8\varphi)$  term is required to reproduce the gap minima observed around  $0^\circ$  and  $45^\circ$ . As shown in Fig. 4A, we find that this simple analysis successfully explains the experimental data (24). The obtained gap functions are depicted in Fig. 4B. The nodal points in the middle FS are located at  $\varphi = \pm(5.34 \pm 0.04)^\circ$  (fitting parameters are in Table 1). We have confirmed that these gap functions are consistent with the London penetration depth results (fig. S9). Thus, we conclude that K122 is a nodal *s*-wave multi-gap superconductor with unusual eight-fold sign reversal in a gap function. This implies that in spite of the large variety of gap functions even within the 122 family, the basic symmetry of the superconducting order parameter always belongs to the  $A_{1g}$  representation, which is symmetrical with respect to fourfold rotation (25).

On the basis of the above results of the SC-gap structure in K122, it was important to ensure that surface effects can be excluded in our observations. It is widely accepted that laser ARPES using very low-energy photons ( $h\nu = 6.998$  eV, as in the present case) is bulk-sensitive, which is in contrast to conventional ARPES measurements that use higher-energy photons. We have further checked that the FS size of the present compound K122 determined with our laser ARPES is nearly same as those determined with de Haas-van Alphen oscillations, which measures bulk properties (15). Moreover, the determined SC-gap structure well reproduces the previously reported London penetration depth results (fig. S9). In addition, we have performed systematic measurements of the FSs, MDCs, and EDCs at  $T = 10$  K (figs. S10 and S11), which indicate very good consistency with the data measured below  $T_c = 3.4$  K. These results confirm that our measurements do indeed probe the bulk electronic structure and FSs, thus ensuring that surface effects can be safely excluded in our observations.

Given the importance of intra- and interorbital interactions and proximity of the FSs in momen-



**Fig. 3.** (A) EDCs and (B) symmetrized EDCs at  $k_F$  of the middle FS for  $\varphi = 8.9^\circ, 4.0^\circ$ , and  $-0.5^\circ$  are indicated by red, blue, and green symbols, respectively. The fits to the Dynes' function are indicated by the solid lines in (A and B), and the estimated SC-gap sizes are listed in (B). (C and D) Temperature-dependent EDCs above and below  $T_c$  (C) near the nodal point ( $\varphi = 5.0^\circ$ ) and (D) for an off-nodal point ( $\varphi = 22.7^\circ$ ).

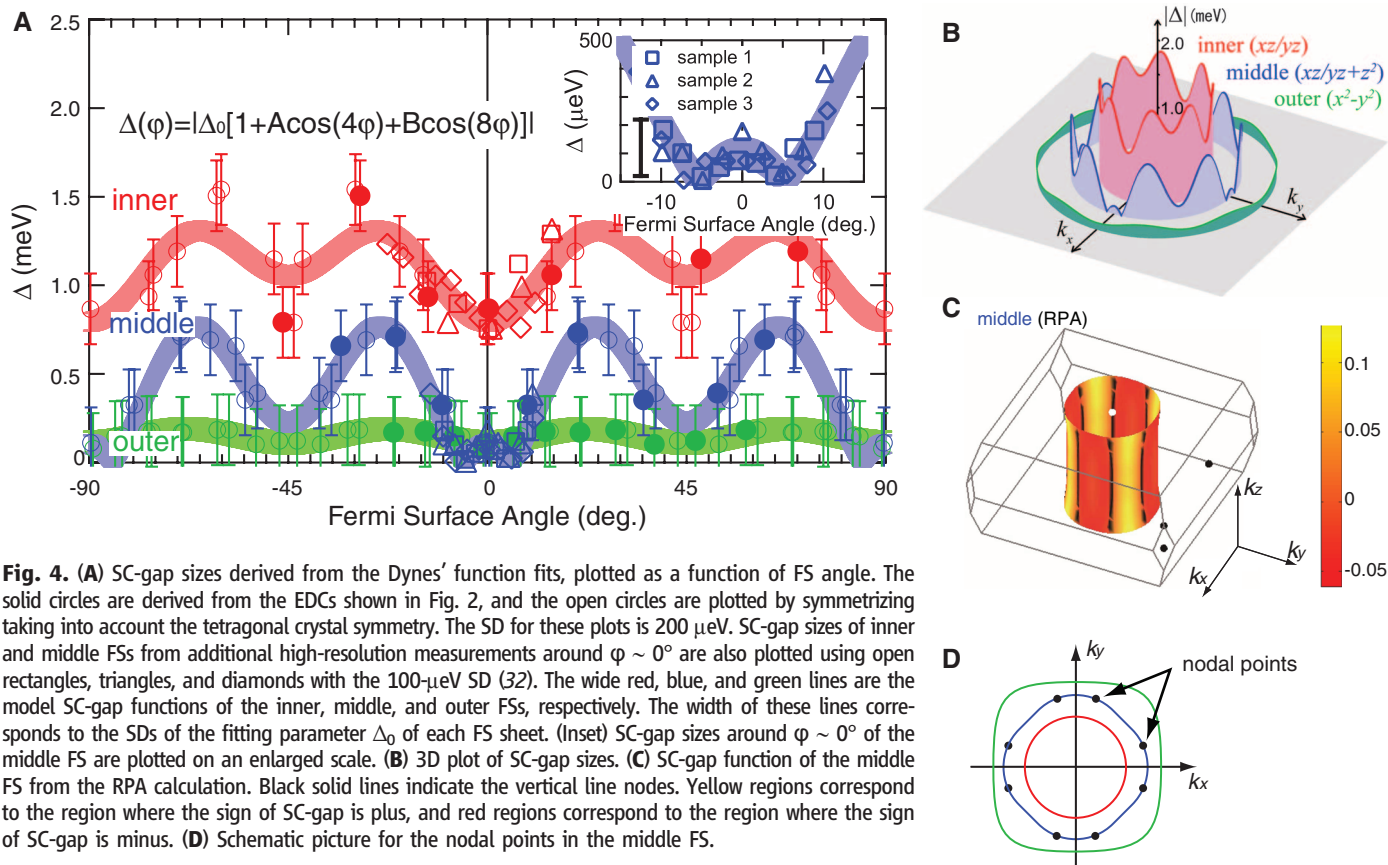
**Table 1.** Fitting parameters for Fig. 4A.  $k_B$  is the Boltzmann constant.

|           | $\Delta_0$ (meV) | $2\Delta_0/k_B T_c$ | A                | B                |
|-----------|------------------|---------------------|------------------|------------------|
| Inner FS  | $1.11 \pm 0.05$  | $7.58 \pm 0.34$     | $-0.12 \pm 0.06$ | $-0.17 \pm 0.05$ |
| Middle FS | $0.41 \pm 0.05$  | $2.80 \pm 0.34$     | $-0.40 \pm 0.14$ | $-0.85 \pm 0.18$ |
| Outer FS  | $0.15 \pm 0.06$  | $1.02 \pm 0.41$     | $-0.01 \pm 0.57$ | $-0.26 \pm 0.58$ |

tum space (10, 11, 26, 27), the almost-zero gap on the outer FS and the largest gap on the inner FS compared with the middle FS may seem inconsistent at first glance. However, we believe that this is quite consistent with the multi-orbital character of the FSs of iron-based superconductors: The inner and middle FSs have a predominantly  $xz/yz$  and  $xz/yz + z^2$  character, respectively. The existence of strong FS-sheet dependence in the SC-gap size and the presence of SC-gap nodes may indicate that there is some frustration between competing pairing interactions on the hole FSs. This can be consistently explained by considering inter- and intra-band repulsive interactions mediated by spin fluctuations (11, 26, 27) as follows. Although we have not measured the FS near the zone corner, it has been suggested both experimentally and theoretically that the interband scattering between the zone-center bands and the zone-corner bands can still be important (28). In (28), incommensurate spin fluctuations have been observed by means of inelastic neutron scattering with a wave vector approximately corresponding to that from the BZ center ( $\Gamma$  point) to the BZ corner ( $X$  point). The middle FS has finite con-

tributions from the  $z^2$  orbital, whereas the clover-like FSs at  $X$  point have almost no contribution from this orbital (Fig. 4B and fig. S5). Hence, the  $z^2$ -orbital component in the middle FS has no counterpart for the sign change of SC gap in the clover-like FSs. As a result, an intra-FS sign change may be preferable for the SC gap of the middle FS around the momentum region with a large  $z^2$  orbital contribution. This scenario can also explain the SC-gap size of the inner and outer FSs. From the density functional theory calculations, the dominant contributions to the clover-like FSs are  $xz/yz$  orbitals. Because the inner FS also has dominantly  $xz/yz$  character, the inter-FS pairing interactions should be the strongest leading to the largest gap size for the inner FS. For the outer FS having large  $x^2 - y^2$  orbital contribution, the corresponding contribution is almost absent in the partner clover-like FSs, which is consistent with the negligibly small gap size on the outer FS, as observed in this study. In addition, this band has a relatively large renormalization effect (15), which may reduce the gap size.

In a recent study investigating the relation between spin fluctuations and superconductivity,



**Fig. 4.** (A) SC-gap sizes derived from the Dynes' function fits, plotted as a function of FS angle. The solid circles are derived from the EDCs shown in Fig. 2, and the open circles are plotted by symmetrizing taking into account the tetragonal crystal symmetry. The SD for these plots is 200  $\mu\text{eV}$ . SC-gap sizes of inner and middle FSs from additional high-resolution measurements around  $\varphi \sim 0^\circ$  are also plotted using open rectangles, triangles, and diamonds with the 100- $\mu\text{eV}$  SD (32). The wide red, blue, and green lines are the model SC-gap functions of the inner, middle, and outer FSs, respectively. The width of these lines corresponds to the SDs of the fitting parameter  $\Delta_0$  of each FS sheet. (Inset) SC-gap sizes around  $\varphi \sim 0^\circ$  of the middle FS are plotted on an enlarged scale. (B) 3D plot of SC-gap sizes. (C) SC-gap function of the middle FS from the RPA calculation. Black solid lines indicate the vertical line nodes. Yellow regions correspond to the region where the sign of SC-gap is plus, and red regions correspond to the region where the sign of SC-gap is minus. (D) Schematic picture for the nodal points in the middle FS.

random phase approximation (RPA) was used to obtain the spin susceptibility and solve the linearized Eliashberg equation (29), showing that the FS with substantial  $z^2$  contribution has a horizontal node around  $k_z = \pi$ . However, recently, it has been shown that horizontal nodes can appear on the middle FS by a phenomenological calculation (25). By RPA calculation, we also found that the horizontal node on the middle FS around  $k_z = \pi$  becomes loop nodes and eventually vertical nodes if we introduce an orbital-dependent potential that mimics the self-energy effect (Fig. 4C and fig. S6). From a comparison with the three-dimensional (3D) ARPES study of Yoshida *et al.* (16), we conclude that the  $k_z$  value for our 7-eV photon is very close to  $\pi$  (30). If the nodal lines make a loop around  $k_z = \pi$ , the SC-gap nodes should be smeared out because of the  $k_z$  broadening effect (31). Therefore, the nodal lines are likely running almost vertically around the FS angle  $\varphi \sim \pm 5^\circ$  (Fig. 4D).

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be broader for azimuth angle =  $45^\circ$ . However, the MDC width of the middle FS at  $E_F$  is not so different between that for azimuth angle =  $0^\circ$  and for azimuth angle =  $45^\circ$ , thus confirming that our ARPES results using 7-eV photons should trace the region very close to the Z point.

- Because the escape depth of the photoelectrons is finite,  $k_z$  value of photoelectrons is not conserved but is broadened.  $k_z$  value of the observed photoelectrons should be integrated within 10 to 20% of the whole BZ region, considering that the escape depth of photoelectrons for 7-eV laser is  $\sim 30$  to  $70$  Å, whereas the unit cell length along the c axis is  $\sim 14$  Å.
- We have confirmed that SD of the SC-gap value obtained through least-square fitting is below 1  $\mu\text{eV}$  by assuming that the detected counts of photoelectrons obey Poisson distribution.

**Acknowledgments:** We thank K. Kuroki, T. Yoshida, and S. Kittaka for valuable discussions; A. V. Chubukov for valuable comments; and T. Kondo for reading the manuscript and comments. This research is supported by the Japan Society for the Promotion of Science (JSPS) through its FIRST Program. C.H.L. was additionally supported by Grant-in-Aid for Scientific Research (No. 24340090) from JSPS. H.F. was additionally supported by Grants-in-Aid for Scientific Research (21540351 and 22684016) from the Ministry of Education, Culture, Sports, Science and Technology (MEXT) and JSPS and Innovative Areas "Heavy Electrons" (20102005 and 21102505) from MEXT. T.S. was additionally supported by Grant-in-Aid for the Global COE program "The Next Generation of Physics, Spun from Universality and Emergence" from MEXT, and KAKENHI from JSPS.

#### Supplementary Materials

[www.sciencemag.org/cgi/content/full/337/6100/1314/DC1](http://www.sciencemag.org/cgi/content/full/337/6100/1314/DC1)  
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Tables S1 and S2  
References (33–43)

3 April 2012; accepted 25 July 2012  
10.1126/science.1222793



# Relaxation and Prethermalization in an Isolated Quantum System

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Understanding relaxation processes is an important unsolved problem in many areas of physics. A key challenge is the scarcity of experimental tools for the characterization of complex transient states. We used measurements of full quantum mechanical probability distributions of matter-wave interference to study the relaxation dynamics of a coherently split one-dimensional Bose gas and obtained comprehensive information about the dynamical states of the system. After an initial rapid evolution, the full distributions reveal the approach toward a thermal-like steady state characterized by an effective temperature that is independent from the initial equilibrium temperature of the system before the splitting process. We conjecture that this state can be described through a generalized Gibbs ensemble and associate it with prethermalization.

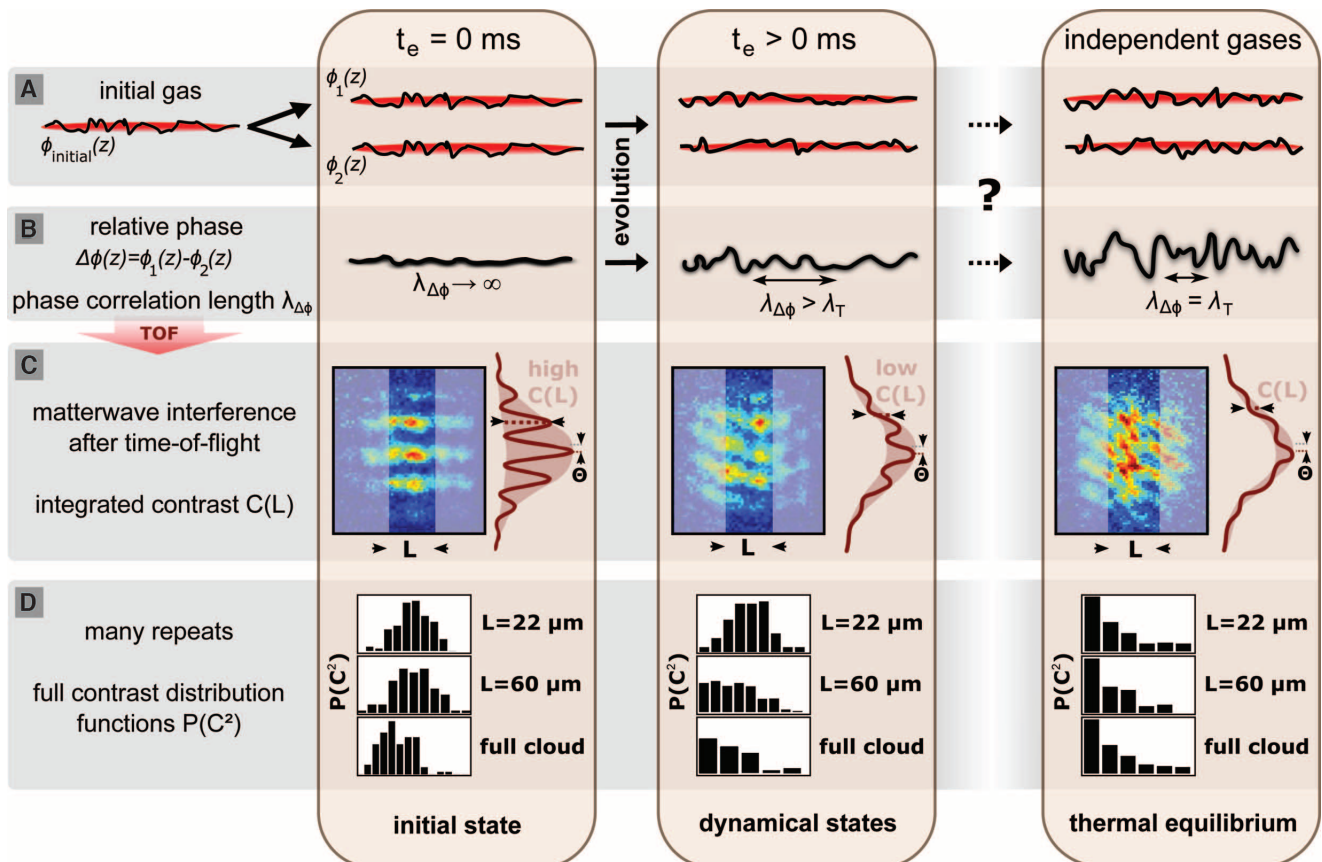
**D**espite its fundamental importance, a general understanding of how isolated quantum many-body systems approach thermal equilibrium is still elusive. Theoretical concepts

such as the quantum ergodic theory or the eigenstate thermalization hypothesis (1–3) infer requirements for a system to be able to undergo relaxation, but it is still unclear on what time scale

this occurs. In situations in which conservation laws inhibit efficient relaxation, many-body systems are expected to display a complex behavior. An intriguing phenomenon that has been suggested in this context is prethermalization (4), a general concept that is predicted to be applicable to a large variety of physical systems (5–9). In the present understanding, prethermalization is characterized by the rapid establishment of a quasi-stationary state that already exhibits some equilibrium-like properties. Full relaxation to the

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**Fig. 1.** (A) An initial-phase fluctuating 1D Bose gas is split into two uncoupled gases with almost identical phase distributions  $\phi_1(z)$  and  $\phi_2(z)$  (black solid lines) and allowed to evolve for a time  $t_e$ . (B) At  $t_e = 0$  ms, fluctuations in the local phase difference  $\Delta\phi(z)$  between the two gases are very small, and the corresponding phase correlation length is very large. During the evolution, these relative-phase fluctuations increase, and the correlation length decreases. The main question we address is whether or when this system will reach the corresponding thermal equilibrium of uncorrelated phases as characterized by the initial temperature  $T$  and thermal coherence length  $\lambda_T$ . In experiment, this situation can be prepared on purpose by splitting a thermal

gas and cooling it into two independent gases (32). (C) Typical experimental matter-wave interference patterns obtained by overlapping the two gases in time-of-flight after different evolution times. Differences in the local relative phase lead to a locally displaced interference pattern. Integrated over a length  $L$ , the contrast  $C(L)$  is a direct measure of the strength of the relative-phase fluctuations. (D) Because of the stochastic nature of the phase distributions, repeated experimental runs yield a characteristic distribution  $P(C^2)$  of contrasts, which allows one to distinguish between the initial state, an intermediate prethermalized state, and the true thermal equilibrium of the system.

thermal equilibrium, if present at all, is expected to occur on a much longer time scale. It is conjectured that prethermalized states can be described by equilibrium statistical mechanics through a generalized Gibbs ensemble (*1, 3, 10*). Here, we present a direct observation of such a state.

Systems of ultracold atoms provide exceptional opportunities to experimentally study such nonequilibrium problems because of their almost perfect isolation from the environment. Moreover, the time scales for internal relaxation processes (collisions) are easily accessible in experiments. Consequently, there recently have been various studies about nonequilibrium dynamics in ultracold atom systems (*11–16*).

One-dimensional (1D) Bose gases are of particular interest because they inherently contain strong fluctuations and dynamics: At finite tem-

perature, many longitudinal modes of the system are populated, which manifests itself in the rich spatial structure and dynamics in their local phase. This is in stark contrast with 3D condensates, in which the existence of long-range order allows the characterization of the state with a single, global phase. In addition, a homogeneous 1D Bose gas is a prime example of an integrable quantum system (*17*). Approximately realizing such systems in the experiment thus opens up the possibility of studying dynamics and relaxation close to an integrable point.

In our experiment (Fig. 1), we started from a single 1D Bose gas of  $^{87}\text{Rb}$  in the quasi-condensate regime (*18*) prepared in an elongated microtrap on an atom chip (*19*). We prepared the initial state for our evolution by rapidly and coherently splitting the single 1D gas, producing a system of two

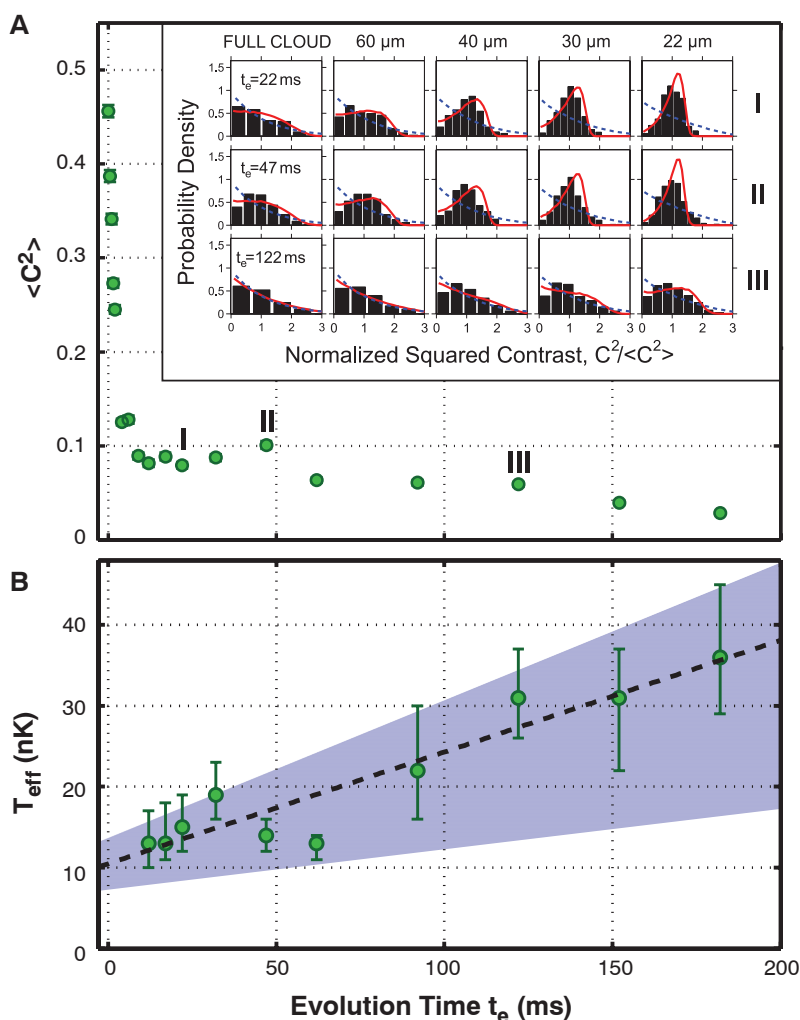
uncoupled 1D Bose gases in a double-well potential. The two trapped 1D gases only differ by the quantum shot-noise introduced in the splitting (Figs. 1A); they have almost identical longitudinal phase profiles. In contrast, two independently created quasi-condensates have vastly different and uncorrelated phase profiles (Fig. 1, right column). The strongly correlated phase of the two gases after splitting reflects the memory that they originally come from a single quasi-condensate. Our experiment studies how this memory about the initial state evolves and decays in time and whether a thermal equilibrium state corresponding to two independent and classically separated quasi-condensates is reached in the evolution.

We probed the evolution of the local phase difference between the two quasi-condensates by using matter-wave interference (Fig. 1C). The system is allowed to evolve in the double-well for some evolution time  $t_e$  before the two 1D gases are released from the trap and allowed to interfere in time-of-flight. The local phase difference along the axial length of the system directly translates to a shift of the interference peaks along the transverse direction of the gases (Fig. 1C). To probe the strength of the fluctuations in the local phase difference  $\Delta\phi(z)$ , we integrated the interference pattern longitudinally over a variable length  $L$  and extracted from the resultant line profile our main experimental observable: the integrated contrast  $C(L)$  (Fig. 1C). For the initial state, the local phase difference is close to zero everywhere along the quasi-condensates, and thus, the integrated interference contrast  $C(L)$  is large for all integration lengths  $L$ . During the course of the evolution, the phase difference varies in the longitudinal direction as a result of the strong fluctuations inherent in 1D systems, which causes the reduction of  $C(L)$ , starting with long integration lengths. Thus, the measurements of  $C(L)$  allow the characterization of the particular dynamics of 1D quasi-condensates.

The mean squared contrast  $\langle C(L)^2 \rangle$ , similarly to the coherence factor used in (*11*), is a direct measure of the integrated two-point correlation function of the relative phase between the two halves of the system (*20, 21*). Integrating over the whole length of the interference pattern, we observed (Fig. 2A) an initial rapid decay in  $\langle C^2 \rangle$  on a time scale of  $\sim 10$  ms, after which a quasi-steady state emerges that slowly evolves further on a much slower time scale.

The initial rapid decay in Fig. 2A is analogous to the one observed in the experiment presented in (*12*), which was limited to  $t_e < 12$  ms by longitudinal dynamics introduced in the splitting. Substantial improvements in the experimental techniques (*22*) allowed us to reveal the long-time behavior. We will first show that this steady state is not the expected thermal equilibrium and associate it with prethermalization (*4*).

To probe the nature of this quasi-steady state, we started by using tools developed to characterize equilibrium systems (*20, 21, 23, 24*) and capture higher-order correlations in the system through the higher moments  $\langle C^{2n} \rangle$ . For this, we extracted



**Fig. 2.** (A) Evolution of the mean squared-contrast  $\langle C^2 \rangle$  for interference patterns integrated over the whole length of the 1D systems. Rapid decay is followed by a long slow further evolution. Error bars are SEs of the mean. (Inset) Experimental nonequilibrium distributions of  $C^2/\langle C^2 \rangle$  at  $t_e = 22, 47$ , and  $122$  ms, respectively (histograms) and a fit of a theoretical equilibrium distributions leading to  $T_{\text{eff}} = 15^{+4}_{-3}, 14^{+2}_{-2}$ , and  $31^{+5}_{-6}$  nK, respectively (red solid line). For comparison, the calculated equilibrium distributions for  $T = 78 \pm 10$  nK (blue dashed line) are added. (B) Evolution of  $T_{\text{eff}}$  for the whole data set extracted by fitting equilibrium distributions. A linear fit indicates an increase of  $T_{\text{eff}}$  over time of  $0.14 \pm 0.04$  nK/ms. The shaded area indicates the measured heating rate of our atom trap of  $0.11 \pm 0.06$  nK/ms.

the full quantum mechanical probability distribution function (FDF)  $P(C^2)dC^2$ , which gives the probability to observe a value  $C^2$  in the interval between  $C^2$  and  $C^2 + dC^2$ . The higher moments  $\langle C^{2n} \rangle$  are directly related to  $P(C^2)$  by  $\langle C^{2n} \rangle = \int C^{2n} P(C^2) dC^2$ . Consequently, the FDF is a direct measure of all even relative-phase correlations between the gases and hence determines the state of the system in detail (20, 21). In particular, high phase coherence between the two halves of the system results in a peaked Gumbel-like distribution, whereas the distribution is exponential in form when the phase coherence is low (20, 21, 23, 24).

Using a statistically large set of data, we were able to map the time evolution of the FDFs for

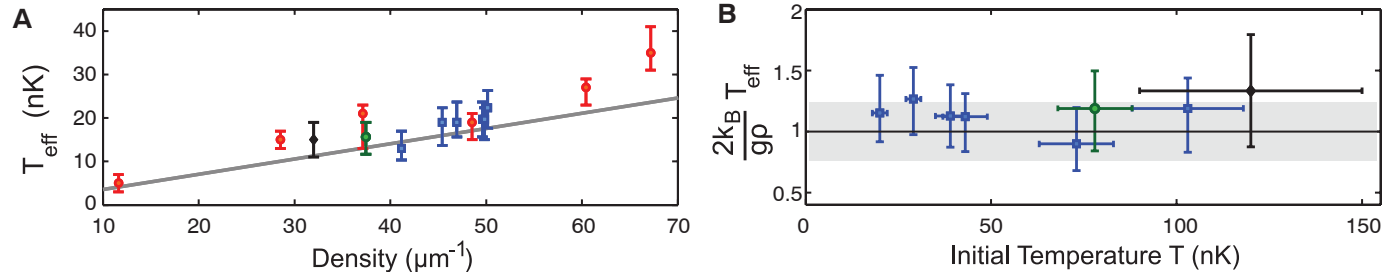
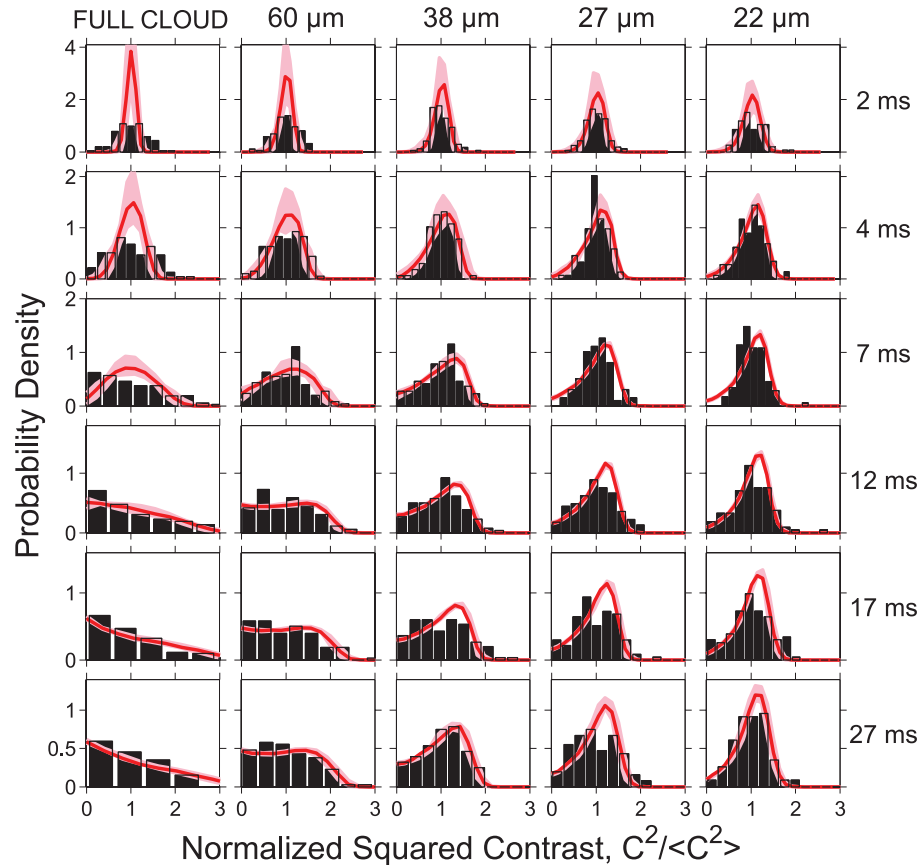
different length scales  $L$ . For times  $>12$  ms—directly after the initial rapid evolution shown in Fig. 2A—we found remarkable agreement of the measured FDFs with theoretical equilibrium distributions. We extracted an effective temperature  $T_{\text{eff}}$  from a simultaneous fit to the measured data on all length scales probed (Fig. 2A, insets). Surprisingly, immediately after the fast decay at  $t_e = 12, 17,$  and  $22$  ms we found  $T_{\text{eff}} = 13 \pm 4, 13 \pm 5,$  and  $15 \pm 3$  nK, respectively, which is roughly a factor of five lower than the initial temperature of the unsplit system ( $T = 78 \pm 10$  nK). The observed steady-state hence cannot be the true thermal equilibrium state of the system. For a direct comparison of the FDFs of the nonequilibrium system with the FDFs of a thermal equilibrium

system, see (22). The interference is sensitive only to the relative degrees of freedom. The initial thermal energy remains stored in the common mode fluctuations of the two halves of the system, which are not probed by the interference pattern.

In contrast, for  $t_e < 12$  ms the shapes of the measured FDFs were not consistent with equilibrium theory. The thermal-like appearance of the state is established only during the evolution of the system.

To analyze the subsequent further slow evolution observed in Fig. 2A, we extracted the effective temperature  $T_{\text{eff}}$  for all times after the initial decay (Fig. 2B). We found an increase of  $T_{\text{eff}}$  over time of  $0.14 \pm 0.04$  nK/ms. This is, however, consistent with the measured heating rate of

**Fig. 3.** The evolution of the squared-contrast distribution  $P(C^2)$  for different integration lengths  $L$ . Experimental data are plotted by using histograms and the theoretical simulations as (red) curves. For integration over the full cloud length, the distribution rapidly becomes exponential with increasing evolution time  $t_e$ . For the shortest integration length, the distribution preserves a nonzero peak, showing a persisting memory of the correlations of the initial state (33). The light (pink) shaded areas denote the errors of the experimentally measured theory input parameters.



**Fig. 4.** (A) Dependence of  $T_{\text{eff}}$  on  $\rho$  and (B) independence of  $T_{\text{eff}}$  from the initial temperature  $T$  of the system before splitting, corrected for the scaling of  $T_{\text{eff}}$  with density. The colors encode different data sets. The (black) solid line corresponds to the theoretical prediction  $k_B T_{\text{eff}} = g\rho/2$ . In (A) and (B), the black data point corresponds to the data set presented in Fig. 3, and the green data point corresponds to the data set presented in Fig. 2.



our atom trap of  $0.11 \pm 0.06$  nK/ms, which we characterized independently using equilibrium quasi-condensates (22). This indicates that either no thermalization is present in this nearly integrable system or, if it is present, that it is a very slow process.

To describe the fast evolution from the splitting to the emergence of the quasi-steady state, we used a fully integrable theory based on a Tomonaga-Luttinger liquid formalism (22, 25, 26). The evolution of the local phase difference between the two halves of the system  $\Delta\phi(z)$  is described by a set of uncoupled collective modes with momentum  $k$ —that is, sound waves, which modulate the relative density and phase at a wavelength  $\lambda = 2\pi/k$  and with an amplitude given by the population of the mode. A sudden splitting creates an equipartition of energy between all the  $k$  modes, which initially are all in phase (22). The rapid evolution of the system seen over the first  $\sim 10$  ms corresponds to the dephasing of these  $k$  modes. The FDFs calculated by this integrable theory (25, 26), by using input parameters independently extracted from the experiment, show agreement without any free parameter (Fig. 3).

The model also predicts a steady state to which the integrable system will relax: The dephasing, along with the equipartition of energy between the  $k$  modes introduced by the fast splitting, results in the FDFs of the quasi-steady state being indistinguishable from those of a system in thermal equilibrium at some effective temperature  $T_{\text{eff}}$ , which is determined by the energy given to the relative degrees of freedom by the quantum shot noise introduced in the splitting. The full calculation gives (26)

$$k_B T_{\text{eff}} = g\rho/2 \quad (1)$$

where  $g = 2\hbar\omega_{\perp}a_s$  is the 1D interaction strength for particles with scattering length  $a_s$  trapped in a tube with transversal confinement  $\omega_{\perp}$ ,  $\rho$  is the 1D density of each half of the system, and  $k_B$  is the Boltzmann constant. For the parameters used in the data presented in Fig. 3, the model predicts  $T_{\text{eff}} = 11 \pm 3$  nK, which is in good agreement with our observations of  $T_{\text{eff}} = 14 \pm 4$ ,  $17 \pm 5$ , and  $14 \pm 4$  nK for the evolution times of 12, 17, and 27 ms, respectively.

Moreover, our integrable model predicts (Eq. 1) that the effective temperature should be linearly dependent on the initial 1D density and independent of the initial temperature. Both of these predictions are confirmed by extending the experiments over a wide range of initial conditions (Fig. 4).

The apparent systematic offset of the experimentally derived  $T_{\text{eff}}$  and the theoretical prediction in Fig. 4, A and B, can be attributed to imperfections in the experimental splitting process, which the model assumes to be instantaneous. This finite-time splitting is also the reason that the agreement between the experiment and theory in Fig. 3 is worse for very early times.

Nevertheless, the first milliseconds of the observed dynamics are well captured by the integrable Luttinger liquid theory. The large number of conserved quantities in this integrable system prevents thermalization. Our experimental realization of a 1D system is, however, not completely integrable and will eventually thermalize.

Dynamics beyond the harmonic Luttinger Liquid model is required to couple symmetric and antisymmetric modes and give rise to thermalization (27). A mechanism that is expected to come into play is interactions of particles that go beyond two-body collisions, such as three-body processes connected with higher radial trapping states (28–30). In our present experiment, these processes that can lead to full thermalization are much slower than the dephasing of the collective modes and thus allow the clear observation of the dynamics dominated by the close-by integrable system. It is of great interest to investigate the physics of thermalization in the future and study, for example, how far away from integrability one has to go to see full thermalization and probe its time scale.

In view of our present analysis, the observed decay of the coherence factor in the experiment of Hofferberth *et al.* (12) has to be reinterpreted. In agreement with our present experiment, it shows the same fast “integrable” dephasing of relative modes in the split 1D system (25, 26, 31) and not full decoherence and thermalization as originally interpreted by comparison with the theoretical description of Burkov *et al.* (22, 27). For the present experiment, even independent of our theoretical model, the observed independence of  $T_{\text{eff}}$  from the initial temperature provides direct experimental evidence that we do not observe thermalization.

The quasi-steady state found in our experiments is not the thermal equilibrium state; nevertheless, it can be described by using an equilibrium model (23). It establishes on a time scale much shorter than the expected thermalization time and furthermore exhibits the properties of the dephased state of the corresponding integrable model (26). We thus conclude that our experiments provide a direct observation of prethermalization, as it is predicted to appear in nonequilibrium systems close to an integrable point (10). That the effective temperature is independent from the kinetic temperature supports the prediction that such a state requires a description by a generalized Gibbs ensemble (1, 3, 10).

Our experiment also directly shows that the two separated many-body systems retain memory of their initial state for a time much longer than the randomization of the global phase would suggest, and that genuine decoherence that would erase the memory did not yet occur—that is, the two 1D systems did not yet emerge as two classically separated entities.

The time scale over which this prethermalized state persists remains an open question. It is directly related to the open problems of how two quantum-mechanically entangled objects reach

classicality, the properties of the hypothetical quantum Kolmogorov-Arnold-Moser theorem (1), and the very nature of thermalization itself.

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**Acknowledgments:** We thank Ch. v. Hagen and M. Göbel for early work on the experimental apparatus and the Vienna group for invaluable discussions and assistance. The atom chip was fabricated at ZMNS, TU Wien by W. Schrenk and M. Trinker. The experiments were supported by the Austrian Science Fund (FWF) through grants P22590-N16 and M1040-N16, the Doctoral Programme CoQuS (W1210), grant

P22590-N16 and the Wittgenstein Prize, and the European Union through the integrating project AQUOTE, Siemens Austria, and the City of Vienna. T.K. and E.D. thank the Army Research Office for funding from the Defense Advanced Research Projects Agency Optical Lattice Emulator program, Harvard-MIT CUA, NSF grant DMR-07-05472, Air Force Office of Scientific Research Quantum Simulation Multidisciplinary

University Research Initiative (MURI), and the Army Research Office-MURI on Atomtronics.

#### Supplementary Materials

www.sciencemag.org/cgi/content/full/science.1224953/DC1  
Materials and Methods

Supplementary Text  
Figs. S1 to S5  
References (34–58)

21 May 2012; accepted 21 August 2012  
Published online 6 September 2012;  
10.1126/science.1224953

# Oxidative Aliphatic C-H Fluorination with Fluoride Ion Catalyzed by a Manganese Porphyrin

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Despite the growing importance of fluorinated organic compounds in drug development, there are no direct protocols for the fluorination of aliphatic C-H bonds using conveniently handled fluoride salts. We have discovered that a manganese porphyrin complex catalyzes alkyl fluorination by fluoride ion under mild conditions in conjunction with stoichiometric oxidation by iodosylbenzene. Simple alkanes, terpenoids, and even steroids were selectively fluorinated at otherwise inaccessible sites in 50 to 60% yield. Decalin was fluorinated predominantly at the C2 and C3 methylene positions. Bornyl acetate was converted to exo-5-fluoro-bornyl acetate, and 5 $\alpha$ -androstane-17-one was fluorinated selectively in the A ring. Mechanistic analysis suggests that the regioselectivity for C-H bond cleavage is directed by an oxomanganese(V) catalytic intermediate followed by F delivery via an unusual manganese(IV) fluoride that has been isolated and structurally characterized.

Biochemistry manifests numerous highly selective transformations of aliphatic C-H bonds into alcohols, halides, and olefins catalyzed by reactive metal-oxo intermediates within enzymes (1, 2). A notable exception is aliphatic C-H bond fluorination: The only fluorinase enzymes yet characterized form C-F bonds by nucleophilic displacement at the preactivated C center of *S*-adenosylmethionine (3, 4). There are no catalytic ways to selectively and directly incorporate fluoride ions into unreactive  $sp^3$  C-H bonds. Yet there is an enormous impetus today to place F at such inaccessible sites in biomolecules and drug candidates. Fluorination of drugs can block sites of phase I metabolism by cytochrome P450 enzymes as well as improving target-binding affinities (5). Further, the incorporation of  $^{18}\text{F}$  into biomolecules can allow direct imaging of metabolic activity and drug targets using the exquisite sensitivity of positron emission tomography (6, 7).

Although strategies for aromatic fluorination developed over the past 5 years have provided access to complex aryl fluorides (8–11), there has been a notable lack of recent progress in the catalytic fluorination of aliphatic C-H bonds (12–14). Direct C-H fluorination with elemental F and electrophilic fluorinating agents, as developed

by Rozen, Sandford, and Chambers (15–17), are viable and very useful methods. Metal-catalyzed direct benzylic C-H fluorination has been achieved recently with palladium catalysts and an “F<sup>+</sup>” source (18). Also, advances in organocatalytic fluorination have enabled enantioselective formation of C-F bonds adjacent to a carbonyl group (19) or to an alcohol, in the latter case via the ring-opening of epoxides with a fluoride nucleophile (20). A chemo-enzymatic fluorination strategy via initial P450-mediated hydroxylation (21) and chemical routes involving initial decarboxylation (22, 23) have also been reported. Despite this impressive progress, a method for the selective and efficient incorporation of F at unactivated C-H sites within a target molecule using fluoride ion is singularly absent from the repertoire of chemical synthesis.

The paradoxical challenge of achieving selective aliphatic fluorination lies in discovering a catalyst that is both sufficiently reactive and predictably selective to transform these ubiquitous yet unactivated  $sp^3$  C-H bonds in the presence of other common functional groups. Such a catalyst would be particularly useful if it could use fluoride ion under convenient laboratory conditions. A strategy was suggested to us by our recent discovery of a C-H chlorination protocol using manganese porphyrin catalysts and hypochlorite ion (24). We considered that site-selective fluorination might be achieved if a suitable fluoride source could be found that redirected the usual biomimetic O rebound scenario (2) to metal-bound fluoride, in the manner of halogenating

metalloenzymes such as SyrB2 that generate an oxo-chloroferrate intermediate (25). Thus, could a manganese fluoride capture substrate radicals generated by oxomanganese-mediated H abstraction? We report here a successful manganese-catalyzed oxidative C-H bond fluorination using fluoride ion.

We have found that a variety of simple alkanes and substituted alkanes, as well as larger natural-product molecules, can be fluorinated effectively in the presence of catalytic amounts of the bulky manganese porphyrin Mn(TMP)Cl (1). This oxidative aliphatic fluorination reaction is driven by iodosylbenzene as the oxo-transfer agent, using silver fluoride/tetrabutylammonium fluoride trihydrate as the fluoride source, both in stoichiometric excess (26). Ultra-dry conditions are not required. Results for the initial exploratory reactions of a panel of simple substrates are presented in Table 1. Cycloalkanes afforded monofluorinated products in ~50% yield. Typically, conversions were ~70%, with small amounts (15 to 20%) of alcohols and ketones also being produced. No products were detected in control experiments that omitted the manganese porphyrin or iodosylbenzene, whereas a ~2:1 ratio of oxygenated to fluorinated products was formed in the absence of tetrabutylammonium fluoride. Only oxygenated products were formed without silver fluoride (27). There were negligible amounts of difluorides produced at this level of conversion, probably due to the electron deficiency of the products induced by the F atom (28). A preliminary investigation of the substrate scope led to the results shown in Table 1 (entries 7 to 12). A range of substituted molecules, including ester, tertiary alcohol, ketone, and amide substituents, proved to be good substrates for fluorination with catalyst 1. Fluorination of methyl cyclohexylcarboxylate (entry 7) and methyl cyclohexanol (entry 8) afforded *trans*-C3 fluorides as the major products. Monosubstituted five- and seven-membered cycloalkanes (entries 9, 10, and 12) were fluorinated exclusively at the C3 and C4 positions, respectively, suggesting subtle stereo-electronic effects on the selectivity of this reaction.

Having demonstrated that it is possible to redirect manganese-catalyzed hydroxylation to fluorination, we next aimed to apply this reaction to larger molecules. The reaction of *trans*-decalin under the same conditions afforded methylene monofluorination products with a 3.5-to-1 preference for C2 over C1 in an overall 51% yield and a 75% conversion (Fig. 1A). Very high methylene regioselectivity was observed for this substrate (>95%), similar to that observed for the manganese-catalyzed chlorination reaction we have

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recently reported (24), suggesting that a similar reactive oxo- or dioxo-manganese(V) intermediate (29) is responsible for the H abstraction step in both reactions.

Likewise, sclareolide, a plant-derived terpenoid with antifungal and cytotoxic activities, afforded C2 and C3 methylene-fluorinated products in an overall 58% yield (Fig. 1B). C2-fluorination was favored by nearly 3:1, probably because of the steric hindrance of the *gem*-dimethyl groups at C4. The products could be separated chromatographically. C2 selectivity has been observed for this substrate by Baran and Eschenmoser for a Rh-catalyzed amination (30, 31) and by White and Chen in a Fe(pdp)/H<sub>2</sub>O<sub>2</sub>-mediated oxidation (32). In contrast, reaction of this molecule using Selectfluor (17) afforded an intractable mixture.

F-substituted steroids, such as dexamethasone and fluasterone, have been found to be beneficial in blocking metabolic pathways (33–35), and <sup>18</sup>F-fluorodihydrotestosterone has shown promise as a radiotracer for imaging prostate cancer in men (36). Because a direct, late-stage steroid fluorination protocol could greatly facilitate such applications, we sought to apply this manganese-catalyzed fluorination reaction to simple steroids. We examined the fluorination of 5 $\alpha$ -androstan-17-one, which contains 28 unactivated *sp*<sup>3</sup> C-H bonds (Fig. 1C). Analysis of this molecule suggested that the carbonyl group would electronically deactivate ring D. Rings B and C are sterically hindered, leaving the methylene groups of the A ring as the most likely sites for H abstraction. Consistent with this analysis, and de-

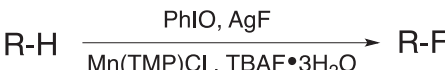
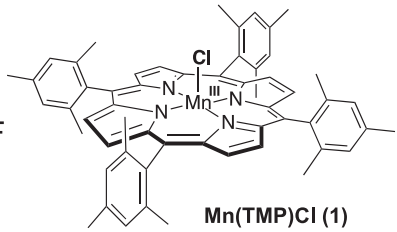
spite the complexity of the molecule, only the C2 and C3 positions in the A ring were fluorinated in an overall yield of 55% (78% of the product distribution at 70% conversion, with minor amounts of oxygenated products). The products of the reaction could be readily separated by column chromatography and structurally assigned by the diagnostic <sup>19</sup>F-nuclear magnetic resonance (NMR) spectrum and the characteristic proton J-couplings (figs. S19 to S22). A 5:1  $\alpha/\beta$  diastereoselectivity was observed for both the C2 and C3 positions, probably reflecting the steric effect of the axial methyl group at C10.

The reaction of bornyl acetate afforded a 55% yield of a single product, *exo*-5-fluoro-bornyl acetate (Fig. 1D). The characterization of this product was based on C-H correlation NMR and <sup>19</sup>F-NMR spectroscopy (figs. S27 to S30) (37). We anticipated that the C5 position of camphor would also be accessible, in analogy to the selectivity of P450cam (CYP101) (38). However, treating camphor under the standard fluorination conditions resulted in 95% recovered starting material. We attribute the low reactivity in this case to the electron-withdrawing carbonyl group, which apparently deactivates the entire molecule toward fluorination, as with the monofluoride products. These results highlight the subtle electronic effects on both the reactivity and selectivity of the fluorination reaction.

We suggest the catalytic cycle shown in Fig. 2A for this manganese porphyrin-catalyzed fluorination, although there are numerous aspects of these transformations that will require further elucidation. Oxidation of the resting Mn(TMP)F catalyst, formed in situ, would afford a reactive oxomanganese(V) species (29), O=Mn<sup>V</sup>(TMP)F, which then abstracts a substrate H atom to produce a C-centered radical and a HO-Mn<sup>IV</sup>-F rebound intermediate. Fluoride binding to separately prepared Mn<sup>IV</sup>(O)(TMP) was indicated by an ultraviolet (UV) spectral shift (423 to 427 nm) that we assign to the formation of [Mn<sup>IV</sup>(O)(F)(TMP)]<sup>+</sup>, in analogy to the well-characterized coordination of hydroxide to Mn<sup>IV</sup>(O) (39).

The key step in forming the fluorinated products is capture of the incipient substrate radicals either by HO-Mn<sup>IV</sup>-F or a *trans*-difluoro-manganese(IV) species. There is no precedent for such a F atom transfer. In this important regard, the fluorination reaction differs from the manganese/hypochlorite chlorinating system we have described (24). Chloride ion is rapidly and reversibly oxidized to hypochlorite by oxoMn<sup>V</sup> porphyrins (40). Although HOF is known (15), there is no evidence that fluoride is oxidized in that way under these conditions. The importance of the hypochlorite in the Mn/OCI case is illustrated by the observation of C-H bromination in the presence of hypobromite, even with a large excess of chloride ion present. We attribute the unusual methylene selectivity observed in both the fluorination and chlorination reactions to stereo-electronically enforced steric clashes between the substrate and the approaching oxoMn<sup>V</sup> catalyst

**Table 1.** Manganese porphyrin-catalyzed fluorination of simple molecules. Reactions were run for 6 to 8 hours at 50°C under N<sub>2</sub> in 3:1 CH<sub>3</sub>CN/CH<sub>2</sub>Cl<sub>2</sub> solvent, 1.5 mmol substrate, 4.5 mmol silver fluoride, 6 to 8 mole % catalyst, 0.3 equivalent of tetrabutylammonium fluoride (TBAF) trihydrate, and 6 to 8 equivalents of iodosylbenzene. Yields were determined by integration of gas chromatography traces using naphthalene as the internal standard. Typical conversions were 70%. Unless otherwise noted, all major fluorination products were isolated as single compounds.


  

  
**Mn(TMP)Cl (1)**

| Entry | Substrate | Fluorination product                | Entry | Substrate | Major fluorination product            | Minor sites                             |
|-------|-----------|-------------------------------------|-------|-----------|---------------------------------------|-----------------------------------------|
| 1     |           | <br><b>2</b> , 49%                  | 7     |           | <br><b>8</b> , 46% dr=6:1             | C4 14%                                  |
| 2     |           | <br><b>3</b> , 51%                  | 8     |           | <br><b>9</b> , 44% dr=8:1             | C4 12%                                  |
| 3     |           | <br><b>4</b> , 55%                  | 9     |           | <br><b>10</b> , 42%                   | C3 11%                                  |
| 4     |           | <br><b>5</b> , 53%<br>1:1.4         | 10    |           | <br><b>11</b> , 51% dr=1.5:1          | C2 <2%                                  |
| 5     |           | <br><b>6</b> , 49%<br>exo: endo=5.7 | 11    |           | <br><b>12a</b> , 30%<br>cis/trans=1:1 | <b>12b</b> , C3<br>27%<br>cis/trans=2:1 |
| 6     |           | <br><b>7</b> , 2:1*                 | 12    |           | <br><b>13</b> , 49% dr=1.6:1†         | C3 9%                                   |

\*Rearranged product identified by the characteristic m-(CH<sub>2</sub>F) peak in the mass spectrum.

†Isolated as diastereomers.

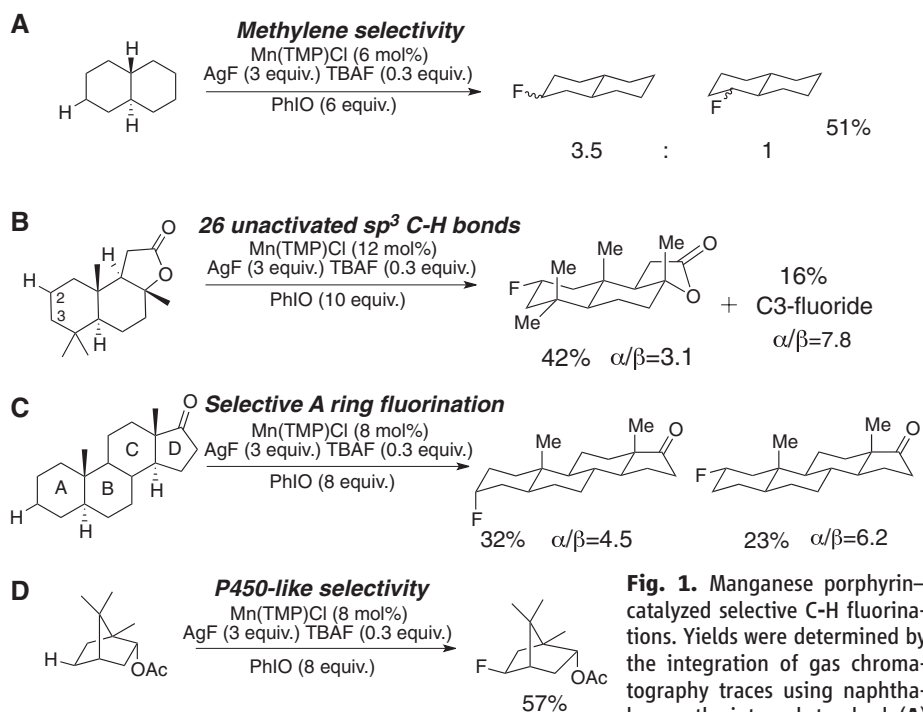


(Fig. 2B). The lowest unoccupied molecular orbitals in a low-spin,  $d^2$  oxoMn<sup>V</sup> complex are expected to be the two orthogonal Mn-O  $\pi^*$  orbitals, which would direct the approach of the scissile C-H bond into a bent  $\pi^*$ -approach trajectory (29, 41).

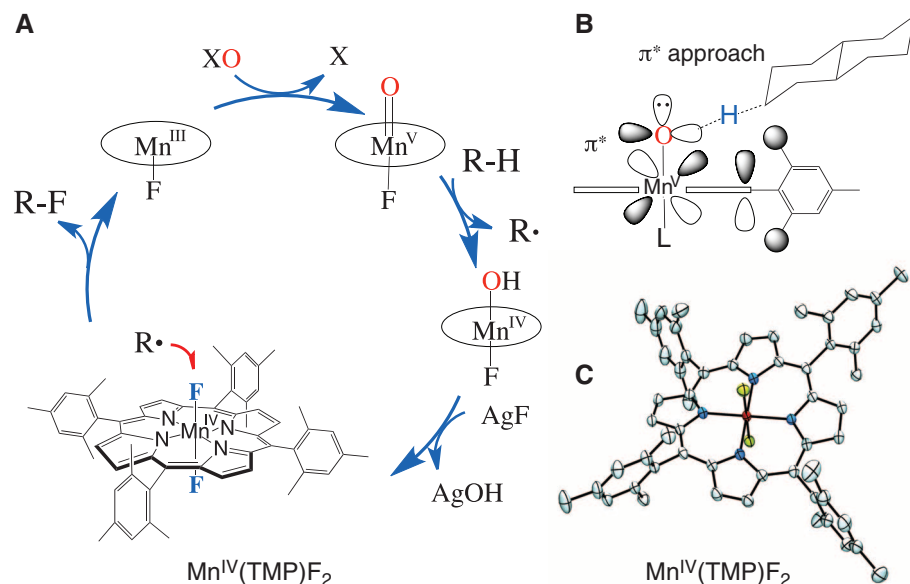
We conducted a number of experiments to examine this mechanistic hypothesis. Initial C-H hydroxylation was ruled out by controls showing that cyclohexanol was oxidized to cyclohexanone under these conditions. No cyclohexylfluoride was detected. Also, the hydroxyl group of 1-methylcyclohexanol is stable to the reaction conditions (Table 1, entry 8). Deuterium kinetic isotope effects (KIEs) were evaluated by the reaction of a 1:1 mixture of cyclohexane and cyclohexane- $d_{12}$ , producing an intermolecular competitive KIE of 6.1. A similar value (5.7) was observed with a mixture of ethylbenzene and ethylbenzene- $d_{10}$ . The large KIE indicates that C-H bond cleavage is the rate-limiting step in the reaction, consistent with typical manganese porphyrin-catalyzed hydroxylation reactions. Furthermore, reaction of norcarane, a diagnostic radical clock substrate (2), afforded 2-fluoronorcaranes and a significant amount of the rearranged fluorinated product, 3-fluoromethylcyclohexene (7), which is indicative of a C radical ring-opening process (Table 1, entry 6). The 2:1 ratio of these cyclopropylcarbinyl and homoallyl fluorides indicates a short radical lifetime of 2.5 ns and rapid trapping of the substrate radicals, given the ring-opening rate constant for the 2-norcaranyl radical of  $2 \times 10^8 \text{ M}^{-1} \text{ s}^{-1}$  (42). We have shown that the chlorination of norcarane with *t*-butyl hypochlorite, also involving diffusing C radical intermediates, gave a similar ratio of rearranged and unrearranged products. Further, the yields of alkyl fluorides were reduced when the reactions were run in air, indicating substrate radical trapping by O<sub>2</sub>.

The identification of *trans*-difluoroMn<sup>IV</sup>(TMP) as the likely fluorinating agent was made possible by its isolation and structural characterization. We were able to obtain pure crystals of the Mn<sup>IV</sup>(TMP)F<sub>2</sub> by treating Mn<sup>IV</sup>(TMP)Cl<sub>2</sub> (43) with excess AgF. The molecular structure of this compound showed two axially bound fluoride ions with F-Mn<sup>IV</sup>-F bond lengths of 1.7931(17) and 1.7968(16) Å (Fig. 2C and tables S1 to S5). These distances are very close to those of diammonium hexafluoromanganate(IV), the only other fluoromanganese(IV) species to be structurally characterized to date (44).

We found that stoichiometric amounts of Mn<sup>IV</sup>(TMP)F<sub>2</sub> could replace silver fluoride in a single-turnover C-H fluorination of cyclooctane using Mn(TMP)Cl and iodosylbenzene. A 43% yield of cyclooctyl fluoride was obtained based on added Mn<sup>IV</sup>(TMP)F<sub>2</sub>. Thermal decomposition of azo-bis- $\alpha$ -phenylethane to generate the phenethyl radical in the presence of Mn<sup>IV</sup>(TMP)F<sub>2</sub> led to a 41% yield of 1-fluoroethylbenzene. These observations indicate that after initial H abstraction, Mn<sup>IV</sup>(TMP)F<sub>2</sub> can trap the substrate radicals in the fluorine delivery step (Fig. 2A). The moderate fluorination yields from these rad-



**Fig. 1.** Manganese porphyrin-catalyzed selective C-H fluorinations. Yields were determined by the integration of gas chromatography traces using naphthalene as the internal standard. (A) Methylene-selective fluorination of *trans*-decalin. (B) Selective fluorination of sclareolide. (C) Selective A-ring fluorination of 5 $\alpha$ -androstan-17-one. (D) Selective 5-exo-fluorination of bornyl acetate.

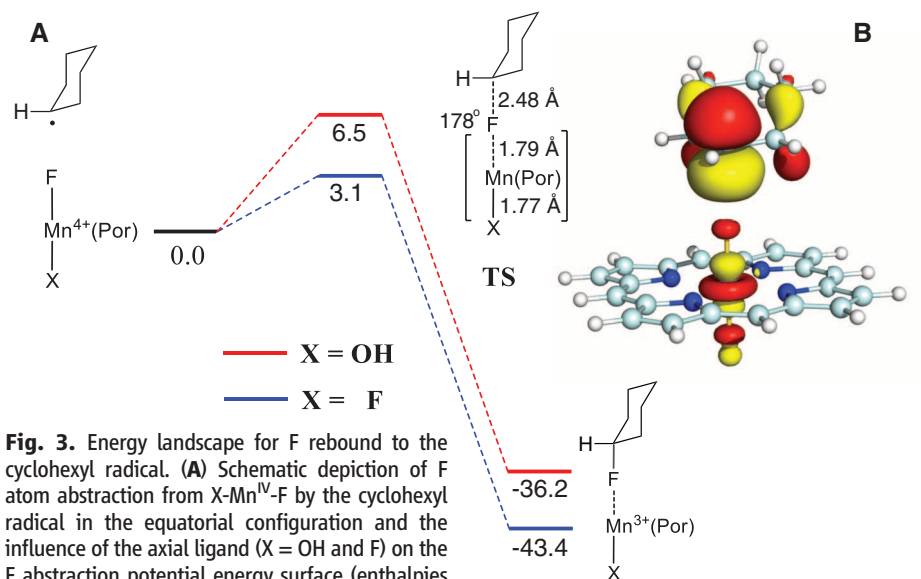


**Fig. 2.** (A) Posited catalytic cycle for manganese porphyrin-catalyzed C-H fluorination reactions. (B) Inferred stereoelectronics for H abstraction. (C) X-ray crystal structure of *trans*-Mn<sup>IV</sup>(TMP)F<sub>2</sub> drawn at 50% probability of the electron density. Highlighted atoms are F (yellow), Mn (magenta), and N (blue) (H atoms are omitted for clarity).

ical trapping experiments are probably due to the falling concentration of the manganese(IV) difluoride under these conditions. Crucial roles for silver fluoride in this scenario under catalytic conditions are first to convert the added Mn(TMP)Cl to the manganese(III) fluoride form of the catalyst and then to replenish the inventory of manganese(IV) fluoride during turnover (26, 27). Although a direct reaction between the substrate

radicals and AgF might also be considered, the reaction between AgF and phenethyl radicals generated in situ from azo-bis- $\alpha$ -phenylethane afforded only trace amounts of fluorinated products.

We have explored the potential energy landscape and electronic structures of the intermediates and transition states proposed in Fig. 2A using density functional theory (DFT) computations and a polarizable continuum solvation model.



**Fig. 3.** Energy landscape for F rebound to the cyclohexyl radical. **(A)** Schematic depiction of F atom abstraction from X-Mn<sup>IV</sup>-F by the cyclohexyl radical in the equatorial configuration and the influence of the axial ligand (X = OH and F) on the F abstraction potential energy surface (enthalpies in kilocalories per mole at 298 K). Bond distances are calculated for X = F. **(B)** Frontier orbital depiction of the transition state (TS) for F transfer.

We found that F atom transfer from Mn(THP)F<sub>2</sub> to a cyclohexyl radical in the equatorial configuration was predicted to occur with a surprisingly low activation barrier of only 3 kcal/mol (Fig. 3), which is very similar to the O rebound barrier for hydroxylation reactions catalyzed by oxomanganese porphyrins. A slightly higher transition state was located for the delivery of F to a cyclohexyl radical in an axial configuration (4.2 kcal/mol). Further, the calculated barrier for F transfer was ~3 kcal/mol lower for the *trans*-difluoromanganese(IV) species (Fig. 3, X = F) than for the analogous hydroxy-fluoride (Fig. 3, X = OH), implicating a much faster reaction rate for the difluoride. Consistent with this low barrier for F transfer, the transition state is very early in the reaction trajectory, showing an exceedingly long C-F distance of 2.48 Å and a Mn-F distance that is only very slightly elongated from the starting manganese(IV) difluoride (TS in Fig. 3 and fig. S31). The visible spectrum of the reaction mixture was complex, apparently due to the presence of several forms of the catalyst during turnover. However, the good yield of 1-fluoroethylbenzene from the generation of phenethyl radical in the presence of Mn(TMP)F<sub>2</sub> provides experimental support for these computational predictions that manganese(IV) fluorides of this type are excellent radical fluorinating agents.

We are encouraged by the promising initial results described here for the selective fluorination of simple hydrocarbons, substituted cyclic molecules, terpenoids, and steroid derivatives. The yields are sufficiently high and the techniques sufficiently simple that the reaction can be performed without specialized apparatus or complicated precautions, other than the normal care that should be taken whenever strong oxidants or fluoride-containing reagents are used. Given that the source of F in this one-step, one-pot protocol

is fluoride ion, we anticipate the potential application of these techniques to the incorporation of <sup>18</sup>F into a wide variety of biomolecules and synthetic building blocks. Moreover, the isolation, structural characterization, and reactivity of the *trans*-difluoromanganese(IV) porphyrin, Mn<sup>IV</sup>(TMP)F<sub>2</sub>, suggest the existence of a rich chemistry of such transition-metal fluorides for the delivery of F substituents.

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- The excess of iodosylbenzene typically used in metalloporphyrin oxidations is due to the competing disproportionation of this reagent, which produces unreactive iodoxybenzene. The requirement for excess fluoride ion appears to derive from the stoichiometry of the fluorination reaction, which also produces hydroxide ions. AgF converts Mn-OH to Mn-F species and Ag<sub>2</sub>O.
- The need for both AgF and tetrabutylammonium fluoride apparently derives from the limited solubility of AgF in the reaction medium and the need for a higher fluoride ion concentration than can be maintained by AgF alone. The UV-visible  $\lambda_{\text{max}}$  observed for (TMP)Mn<sup>III</sup>-Cl (**1**) (475 nm) changed immediately to that of a mixture of (TMP)Mn<sup>III</sup>-F (453 nm) and [(TMP)Mn<sup>III</sup>(F)<sub>2</sub>]<sup>-</sup> (440 nm) under the reaction conditions.
- The high selectivity for monofluorination, the low reactivity of C-H bonds near carbonyl groups, and the limited reactivity of the solvents as well as the tetrabutylammonium ion seem to reflect a very strong polar effect in the C-H bond cleavage step in this reaction.
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**Acknowledgments:** We are grateful to NSF (grants CHE-0616633 and CHE-1148597 to J.T.G.) for support of this research. DFT calculations, hydrocarbon C-H activation, and the CalTech-Princeton collaboration were supported by the Center for Catalytic Hydrocarbon Functionalization, an Energy Frontier Research Center, U.S. Department of Energy, Office of Science, Basic Energy Sciences, under award no. DE-SC0001298 to W.A.G. and J.T.G. A patent application has been filed through Princeton University on methods and catalysts presented in this paper. We thank S. Semproni for assistance with the x-ray crystal structure of Mn<sup>IV</sup>(TMP)F<sub>2</sub>, data for which are available free of charge from the Cambridge Crystallographic Data Centre under reference no. CCDC 893742.

#### Supplementary Materials

www.sciencemag.org/cgi/content/full/337/6100/1322/DC1  
Materials and Methods  
Figs. S1 to S31  
Tables S1 to S6  
References (45–58)

23 March 2012; accepted 26 July 2012  
10.1126/science.1222327

# Bond-Order Discrimination by Atomic Force Microscopy

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We show that the different bond orders of individual carbon-carbon bonds in polycyclic aromatic hydrocarbons and fullerenes can be distinguished by noncontact atomic force microscopy (AFM) with a carbon monoxide (CO)-functionalized tip. We found two different contrast mechanisms, which were corroborated by density functional theory calculations: The greater electron density in bonds of higher bond order led to a stronger Pauli repulsion, which enhanced the brightness of these bonds in high-resolution AFM images. The apparent bond length in the AFM images decreased with increasing bond order because of tilting of the CO molecule at the tip apex.

**B**ond order is an important concept to predict geometry, stability, aromaticity, reactivity, and electronic structure of covalently bonded molecules. The bond order is closely related to the bond length, which, in general, decreases with increasing Pauling bond order (1, 2). If single crystals are available, the bond

length can be determined experimentally with high accuracy using diffraction methods, which—for instance, in the case of fullerenes ( $C_{60}$ ), as predicted by Clar's sextet theory—showed two kinds of bonds of different lengths (3–6). In contrast to diffraction-based techniques, which yield values averaged over large ensembles of molecules,

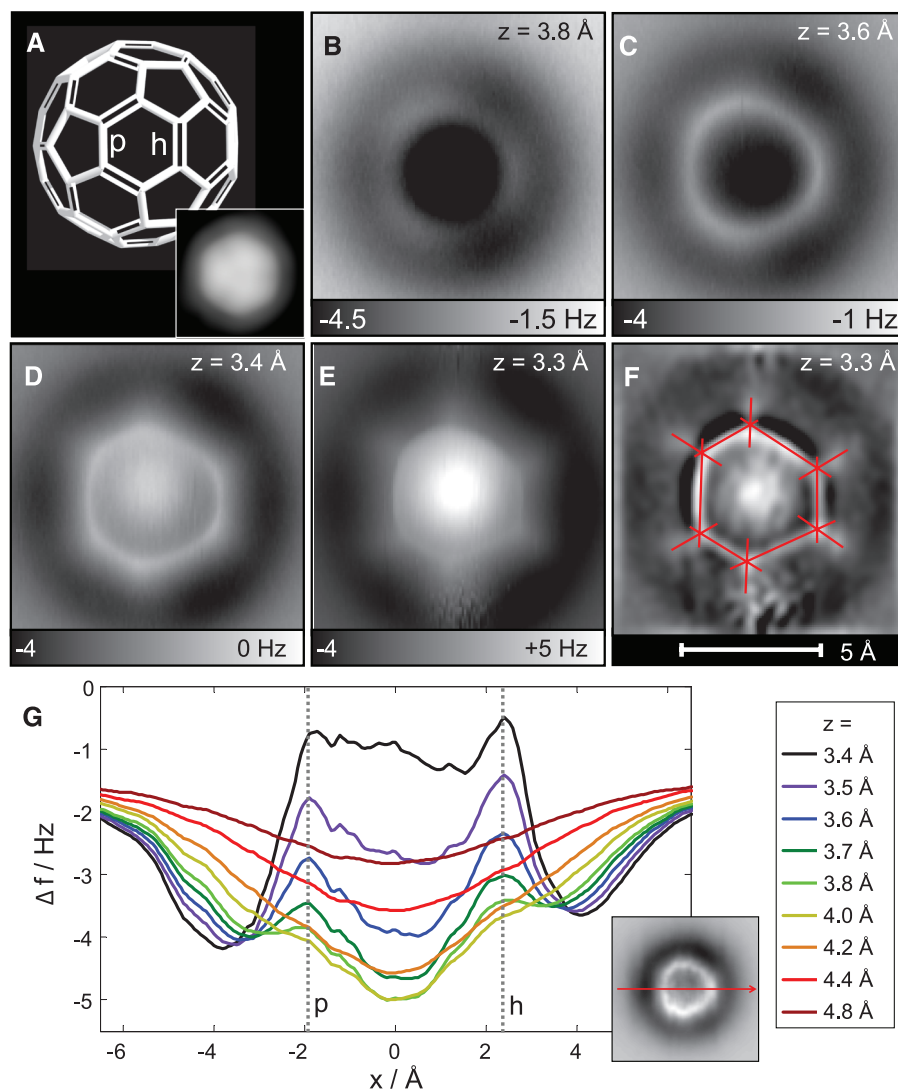
scanning probe microscopy offers the possibility of studying single bonds in individual molecules.

Recently, rapid progress has been reported in the field of noncontact atomic force microscopy (NC-AFM), including the chemical identification of individual surface atoms (7), atomic resolution of carbon nanotubes (8),  $C_{60}$  (9), and planar organic molecules (10). For molecules, not only the chemical species of their constituent atoms can differ, but also the coordination number of atoms, the bond angles, bond order, and bond length. In polycyclic aromatic hydrocarbons (PAHs), the differences in bond order and length are subtle, but detecting these differences is useful for rationalizing aromaticity and reactivity of such molecules (11). AFM offers the possibility of studying systems in which single crystals needed for diffraction methods cannot be grown. Moreover,

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**Fig. 1.** Measurements on  $C_{60}$ . **(A)**  $C_{60}$  model. The bonds fusing a pentagon and a hexagon ( $p$ ) are of smaller bond order compared with the bonds fusing two hexagons ( $h$ ). (Inset) STM image (sample bias  $V = 0.2$  V, current  $I = 2$  pA, size  $24$  by  $24$  Å<sup>2</sup>). The molecule and tip are identical to those in (B) to (F). **(B to E)** AFM measurements showing  $\Delta f$  at different tip heights  $z$  (27) above  $C_{60}/Cu(111)$  using a CO-functionalized tip. Image size  $10$  by  $10$  Å<sup>2</sup>, oscillation amplitude  $A = 0.36$  Å,  $V = 0$  V. **(F)** Laplace-filtered and flattened image of (E), used to measure the apparent bond length  $L'$  (22). **(G)** Line profiles  $\Delta f(x)$  across a  $p$  and  $h$  bond extracted from a three-dimensional (3D) force map (24). The position of the line profiles is indicated in the inset, showing a map of  $\Delta f$  at  $z = 3.6$  Å, extracted from the same 3D force map. The apparent positions of the  $p$  and  $h$  bonds are indicated by the dotted lines. The  $x = 0$  position corresponds to the molecular center, determined by the minimum of  $\Delta f(x)$  at  $z = 4.8$  Å. Note that  $p$  is located at a smaller absolute value of  $x$  than  $h$  and that  $\Delta f(x_p)$  is smaller than  $\Delta f(x_h)$  for all plotted values of  $z$ , with the maximum difference for  $z = 3.7$  Å.





bond-order determination within individual molecules is desirable for chemical-structure determination (12), the investigation of isomerization reactions where bond order changes (13, 14), and the characterization of structural relaxations around atomic defects in graphene (15–17).

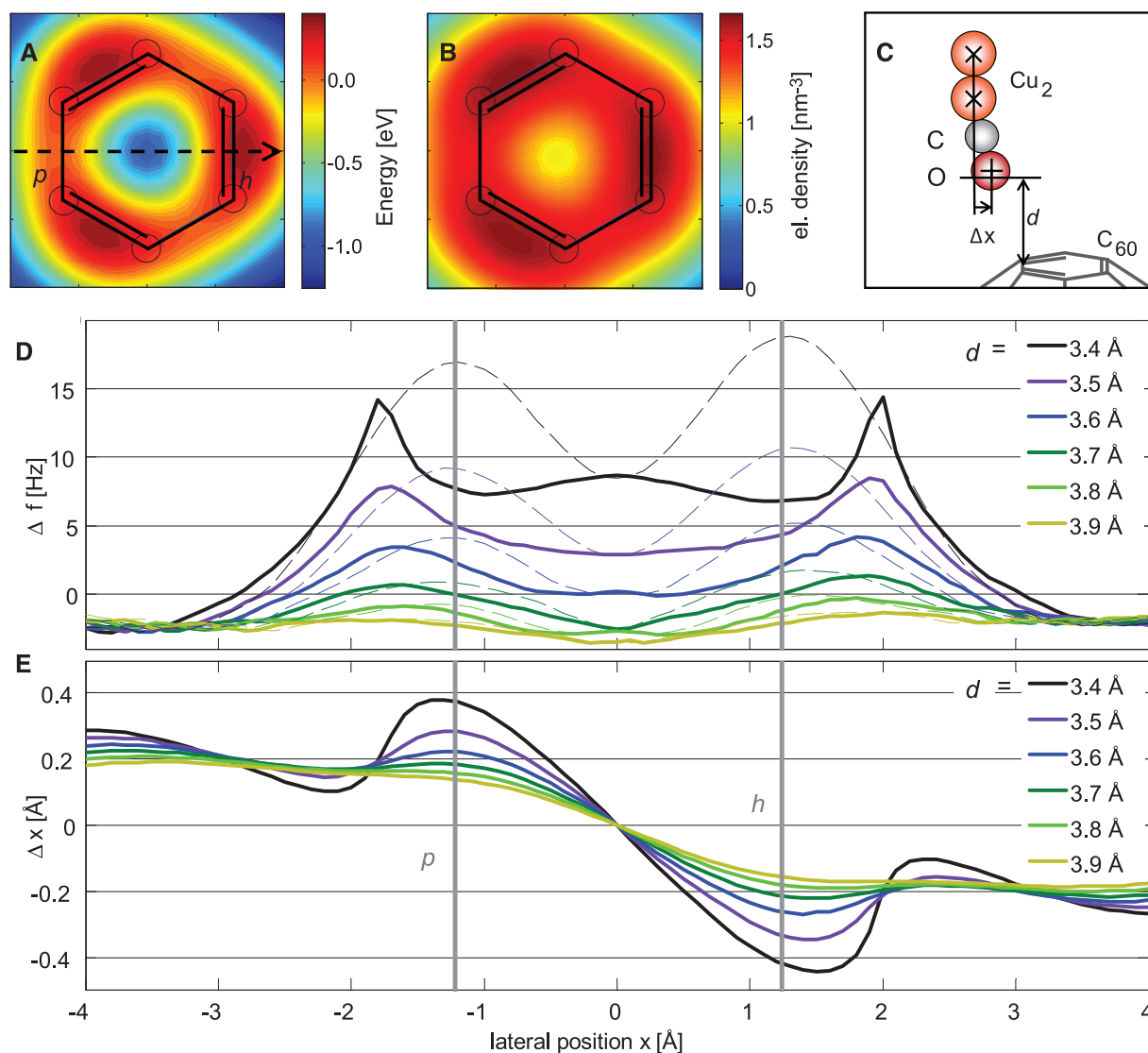
We demonstrated an AFM method to differentiate bond orders and lengths of individual bonds for  $C_{60}$  and large PAHs and investigated C-C bonds parallel to the sample surface. Hence, differences in contrast arising from the chemical species of the atoms (12, 18) or variations of the tip-sample separation (nonplanar adsorption geometries) (12, 19) can be neglected. In a  $C_{60}$  molecule, the bonds fusing two hexagons ( $h$ ) are electron-rich compared with the bonds fusing a pentagon and a hexagon ( $p$ ) (Fig. 1A). The Pauling bond order  $P_b$  of a bond  $b$  in a conjugated molecule is found by counting the number of Kekulé structures (classical resonance

formulas) that show  $b$  as a double bond divided by the total number of different Kekulé structures of the molecule (1, 2). Thus,  $P_b$  can take values between 0 (single bond) and 1 (double bond); in the case of  $C_{60}$ , the Pauling bond orders are  $P_h = 0.44$  and  $P_p = 0.28$ , respectively (20). Correspondingly, theoretical (21) and experimental investigations using neutron diffraction (3), electron diffraction (4), and x-ray diffraction (5, 6) have shown that the bond  $h$  is shorter than the bond  $p$  by  $\sim 5\%$ . The measured bond lengths are  $L_h = 1.38(2)$  Å and  $L_p = 1.454(12)$  Å, respectively (22).

We used a combined scanning tunneling microscopy (STM)/AFM system equipped with a qPlus force sensor (23) operating at 5 K and imaged the molecules with CO-functionalized tips (10, 12, 22, 24). We determined the exact molecular adsorption orientation of  $C_{60}$  on Cu(111) by STM (Fig. 1A, inset) (25, 26). The molecule shown in Fig. 1 exhibited a hexagonal tile and is

oriented as depicted in Fig. 1A. Using NC-AFM, we recorded the frequency shift  $\Delta f$  at constant tip height  $z$  (22, 27), as shown in Fig. 1, B to E. To obtain atomic contrast,  $z$  had to be decreased, usually until  $\Delta f(z)$  reached its minimum above the molecule (in general, at  $z \approx 3.9$  Å), and the contrast increased as  $z$  was further decreased. The smallest tip height where stable imaging conditions could still be maintained was  $z \approx 3.3$  Å (Fig. 1E). The origin of the atomic contrast is Pauli repulsion, which increases with the local electron density, giving rise to the bright features corresponding to the atomic structure of the imaged molecule. The dark halo surrounding the molecules in the AFM images stems mainly from the attractive van der Waals (vdW) force, which shows no corrugation on the atomic scale (10, 28).

Two important observations can be made from the AFM images in Fig. 1. On one hand,  $\Delta f$  is increased above the  $h$  bonds with respect to the



**Fig. 2.** Density functional theory calculations on  $C_{60}$ . Calculated interaction energy between CO and  $C_{60}$  at  $d = 2.9$  Å (A) and electron density of  $C_{60}$  at 2.9 Å above the molecule (B); image size 4 by 4 Å<sup>2</sup>. Using the tip model shown in (C),  $\Delta f(x)$  line profiles along the dashed arrow in (A) were calculated with (solid

lines) and without (thin dashed lines) relaxing the tip geometry, respectively (D). The relaxation resulted in a lateral displacement of the oxygen atom  $\Delta x(x)$ , as shown in (E). The vertical gray lines in (D) and (E) indicate the positions of the  $p$  and  $h$  bonds as expected from the atomic model.

*p* bonds. This effect was best observed for moderate tip heights (Fig. 1B). As can be read off in Fig. 1G by comparing the two local maxima of a line profile  $\Delta f(x)$  across both bonds, we observed the largest  $\Delta f$  difference of  $\sim 0.4$  Hz for  $z = 3.7$  Å. Moreover, in images with atomic resolution, the *h* bonds appear shorter compared with the *p* bonds; this was best observed for the smallest accessible tip heights (Fig. 1, D and E). Figure 1F shows a Laplace filtered image that was used to determine the apparent position of the bonds and

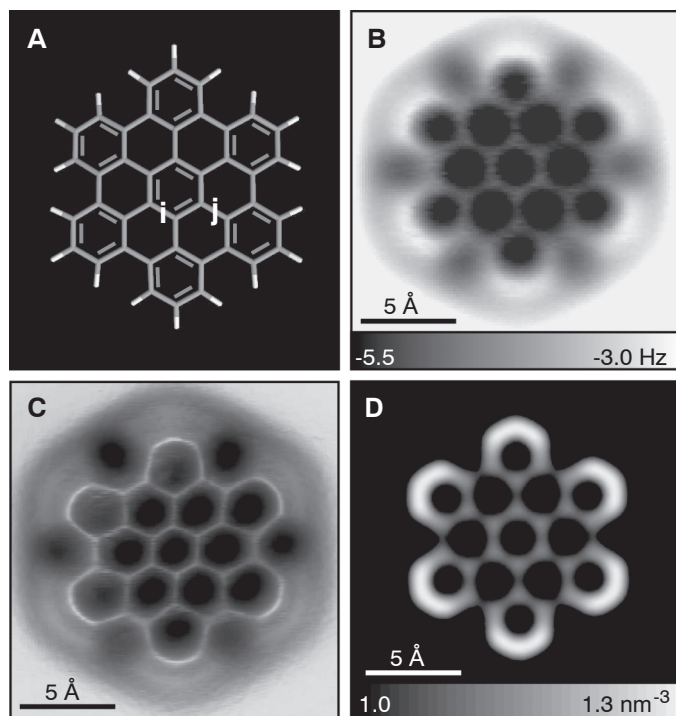
measure the apparent bond length,  $L'_h = 2.0(2)$  Å and  $L'_p = 2.7(2)$  Å, respectively (22). Notably, the apparent bond lengths  $L'$  measured by AFM qualitatively correctly reflect that the *h* bond is shorter than the *p* bond. However, both bonds appear to be substantially longer than they really are, and the difference in the apparent bond lengths of  $\sim 30\%$  is much greater than the real difference of  $\sim 5\%$ .

To understand the contrast mechanisms, we performed density functional theory (DFT) calculations (22). Figure 2A shows an image of the

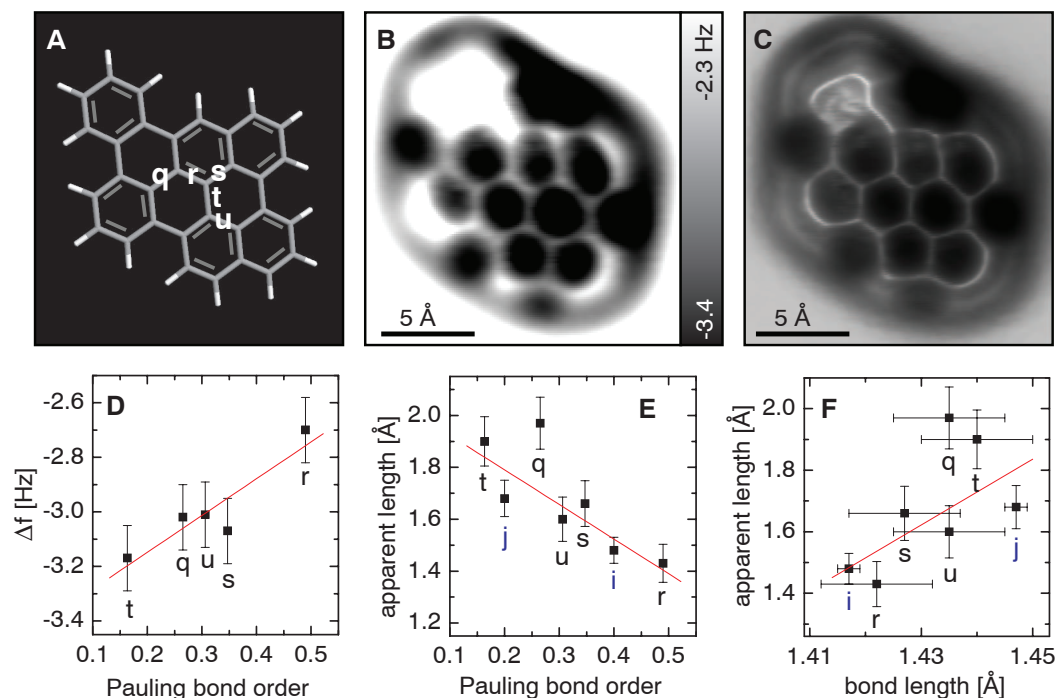
calculated interaction energy for a CO tip at a tip height of  $d = 2.9$  Å, which can be qualitatively compared to the  $\Delta f$  image at  $z = 3.8$  Å (Fig. 1B) (22, 27, 29). The brighter appearance of the *h* bonds with respect to the *p* bonds is well reproduced. The contrast is related to the electron density (shown in Fig. 2B), which increases with bond order. The higher electron density leads to stronger Pauli repulsion; consequently,  $\Delta f$  is increased above bonds with greater bond order.

To account for tip relaxations, especially tilting of the CO molecule at the tip apex (30, 31), we modeled the tip as a  $\text{Cu}_2$  cluster with a CO molecule attached, as shown schematically in Fig. 2C (22). Calculated  $\Delta f(x)$  line profiles (Fig. 2D) without relaxations of the tip structure (dashed lines) show the  $\Delta f(x)$  maxima above the bond positions (vertical gray lines), reflecting the corrugation of the  $\text{C}_{60}$  electron density. Calculations including tip relaxations (solid lines) show a lateral shift of the  $\Delta f(x)$  maxima positions toward greater absolute values of  $x$ , leading to an expansion of the molecule in the image. Moreover, this lateral shift is greater above the *h* bond compared with the *p* bond, in agreement with the experiment. The important tip relaxation for the imaging process is the lateral displacement  $\Delta x(x)$  of the oxygen atom at the tip apex (Fig. 2E) caused by tilting of the CO toward the molecular center because of lateral forces. As this oxygen atom defines the position of our probe, a falling slope of  $\Delta x(x)$  results in an expansion, whereas a rising slope of  $\Delta x(x)$  results in a compression along the  $x$  direction in the particular region of the image. The absolute value of  $\Delta x$  is greater above the *h* bond compared with the *p* bond (Fig. 2E). Hence, the *h* bond appears to be shifted further away from the molecular center than the *p*

**Fig. 3.** Hexabenzocoronene model (A) and constant-height AFM measurements ( $A = 0.35$  Å) on HBC on Cu(111) at  $z = 3.7$  Å (B) and  $3.5$  Å (C). In (C), a pseudo-3D representation is shown to highlight the local maxima. (D) Calculated electron density at a distance of  $2.5$  Å above the molecular plane. Note that *i* bonds are imaged brighter (B) and shorter (C) compared with *j* bonds (22).



**Fig. 4.** Model (A) and constant-height AFM measurements of DBNP on bilayer NaCl on Cu(111) (33) at  $z = 3.6$  Å ( $A = 0.48$  Å) (B and C). A pseudo-3D representation of (B) is shown in (C) to highlight the bonds. Measured values of the frequency shift  $\Delta f$  (D) and the apparent bond length  $L'$  (E) for indicated bonds, including HBC in (E), are plotted as a function of the Pauling bond order. (F) Apparent bond length as a function of the realistic bond length obtained by DFT calculations (for DBNP) (22) and from diffraction data (for HBC) (34). Linear regressions are drawn as a guide to the eye.







# Glacier Extent During the Younger Dryas and 8.2-ka Event on Baffin Island, Arctic Canada

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Greenland ice cores reveal that mean annual temperatures during the Younger Dryas (YD) cold interval—about 12.9 to 11.7 thousand years ago (ka)—and the ~150-year-long cold reversal that occurred 8.2 thousand years ago were ~15° and 3° to 4°C colder than today, respectively. Reconstructing ice-sheet response to these climate perturbations can help evaluate ice-sheet sensitivity to climate change. Here, we report the widespread advance of Laurentide Ice Sheet outlet glaciers and independent mountain glaciers on Baffin Island, Arctic Canada, in response to the 8.2-ka event and show that mountain glaciers during the 8.2-ka event were larger than their YD predecessors. In contrast to the wintertime bias of YD cooling, we suggest that cooling during the 8.2-ka event was more evenly distributed across the seasons.

Summit Greenland ice cores record several abrupt cold excursions that occurred throughout the last glacial period and into the early Holocene (1, 2). Characterized by rapid onset and termination times, the Younger Dryas (YD) and the excursion that occurred 8.2 thousand years ago (ka) are two of the most dramatic examples of abrupt climate change, and consequently their intra- and interhemispheric signature has been the subject of intense focus [e.g., (3, 4)]. Characterizing the extent and magnitude of abrupt climate events beyond their central Greenland stratotypes is critical for understanding the mechanisms that drive abrupt climate change and for understanding how regional climate-system changes are transmitted globally via atmospheric and oceanic teleconnections.

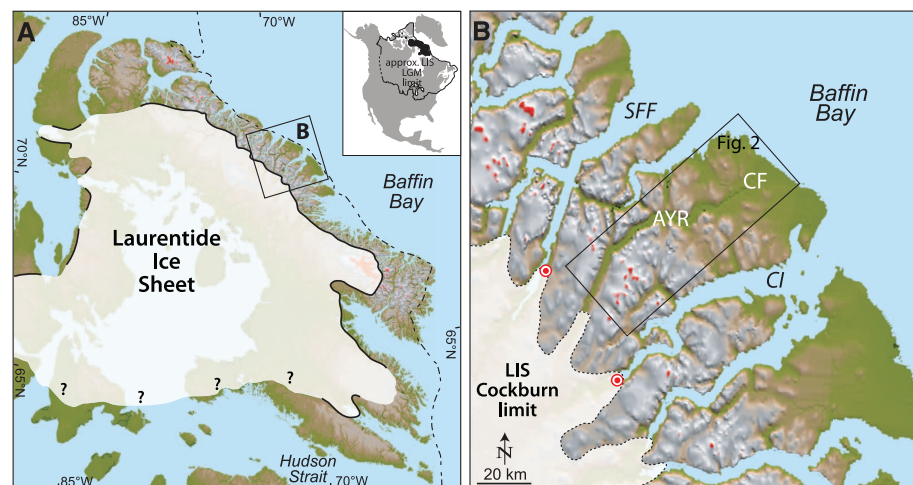
The expression of the YD outside central Greenland has proven particularly puzzling. Even on Greenland, independent terrestrial proxy records that track changes in summer climate do not replicate the extreme temperature depression of the YD depicted in Greenland ice [e.g., (5)]. This disparity has led to the hypothesis that the YD and other abrupt cold reversals in the North Atlantic region were typified by strong seasonality, with cooling primarily restricted to the wintertime and only minimal to moderate summer cooling (6, 7). To test this hypothesis, proxies for terrestrial climate change need to be generated from elsewhere in the North Atlantic region.

Located directly adjacent to Greenland, Baffin Island hosts remnants of the Laurentide Ice Sheet

(LIS) and numerous mountain glaciers whose late glacial to early Holocene histories have remained relatively unexploited compared with their counterparts in Europe [e.g., (8)]. An extensive moraine system deposited along eastern Baffin Island fjord heads was originally believed to demarcate the late Wisconsin maximum extent of the LIS (Fig. 1) (9, 10). Recent work, however, has demonstrated that during the late Wisconsin, the LIS extended to at least the fjord mouths and likely out onto the Baffin Bay continental shelf, with regional deglaciation commencing ~15 to 16 ka (11, 12). Thus, fjord-head moraines represent an advance of the LIS superimposed on deglaciation. Considered correlative with this ice limit are moraines that were deposited by local mountain glaciers that became independent of the LIS during deglaciation (10). Fjord-head moraines are currently dated with conventional

radiocarbon ages from marine fauna that broadly constrain moraine deposition to ~8 to 9.5 thousand calibrated years before the present (cal yr B.P.) (Cockburn Substage) (13); this chronology has remained relatively unchanged for three decades. Here, we precisely date mountain-glacier moraines deposited during the Cockburn Substage on Baffin Island using <sup>10</sup>Be surface exposure dating and compare our new chronology to <sup>10</sup>Be- and <sup>14</sup>C-dated fluctuations of nearby LIS outlet glaciers (Fig. 1).

Our chronology arises from mountain-glacier moraines deposited in Ayr Lake valley after Laurentide ice, which occupied the valley during the last glaciation, retreated during deglaciation. <sup>10</sup>Be ages from the Clyde Foreland and Ayr Lake valley, calculated with a locally constrained <sup>10</sup>Be production rate (14), indicate that the LIS retreated from the Clyde Foreland  $14.1 \pm 1.2$  ka ( $n = 7$  <sup>10</sup>Be ages; mean  $\pm$  1 SD), through Ayr Lake valley at  $13.7 \pm 0.1$  ka ( $n = 3$  <sup>10</sup>Be ages), and well inland of the study area by  $12.7 \pm 0.3$  ka ( $n = 1$  <sup>10</sup>Be ages) (Fig. 2) (14). Thus, tributary glaciers extending from adjacent ice caps flanking Ayr Lake valley disconnected from the LIS outlet glacier ~13.7  $\pm$  0.1 ka. We dated boulders from two correlative moraines deposited in Ayr Lake valley by mountain glaciers during the Cockburn Substage (Fig. 2). Both moraines, ~20 km apart, have mature lichen cover and are situated immediately down-valley of unvegetated, fresh-appearing moraines that we assume were deposited during the late Holocene. <sup>10</sup>Be ages from moraine boulders range from  $17.2 \pm 0.3$  to  $7.9 \pm 0.2$  ka ( $n = 13$  <sup>10</sup>Be ages). Two boulder ages of  $17.2 \pm 0.3$  and  $14.2 \pm 0.3$  ka are >3 SD older than the remaining <sup>10</sup>Be ages and likely contain <sup>10</sup>Be inherited from previous exposure, which is widespread in this region outside of valley bottoms (12, 14). The remaining 11 <sup>10</sup>Be ages indicate that an advance



**Fig. 1.** (A) Late Wisconsin extent of the LIS [dashed line; modified from (12, 35)] and the extent of the fjord-head Cockburn moraine system (9, 10, 13). Green and red on basemaps are lowest and highest elevations, respectively. (B) LIS Cockburn limit in central Baffin Island. AYR, Ayr Lake valley; CI, Clyde Inlet; SFF, Sam Ford Fiord; CF, Clyde Foreland. Red bull's eyes mark the position of 8.2-ka ice-contact deltas in Sam Ford fjord and Clyde Inlet (Fig. 3).

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of mountain glaciers in Ayr Lake valley culminated  $\sim 8.2 \pm 0.2$  ka (Figs. 2 and 3).

Additional  $^{10}\text{Be}$  and  $^{14}\text{C}$  ages from the heads of Clyde Inlet and Sam Ford fjord constrain early Holocene fluctuations of the LIS (Figs. 1B and 3). In Clyde Inlet,  $^{10}\text{Be}$  ages from boulders atop an ice-contact delta range from  $8.6 \pm 0.6$  to  $7.5 \pm 0.8$  ka and have a mean age of  $8.0 \pm 0.4$  ka ( $n = 7$   $^{10}\text{Be}$  ages) (Fig. 3) (15). This age assignment agrees with independent  $^{14}\text{C}$  ages that bracket deposition of the ice-contact delta to between  $8435 \pm 30$  and  $7950 \pm 45$  cal yr B.P. (1 SD) (14). In Sam Ford fjord, numerous  $^{10}\text{Be}$  ages indicate that the majority of the fjord rapidly deglaciated  $9.5 \pm 0.3$  ka but did not deglaciate completely until after  $\sim 7.7$  ka (16). Radiocarbon ages of  $8330 \pm 30$  and  $8210 \pm 190$  cal yr B.P. from an ice-contact delta deposited during the Cockburn Substage mark the timing of a readvance by the LIS outlet glacier occupying Sam Ford fjord (14).

Taken together,  $^{10}\text{Be}$  and  $^{14}\text{C}$  ages from Ayr Lake valley, Clyde Inlet, and Sam Ford fjord indicate that a synchronous advance of mountain glaciers and LIS outlets occurred between  $\sim 8.3$  and  $8.0$  ka, probably driven by the 8.2-ka abrupt cold reversal displayed in Greenland ice cores (Fig. 3). In some locations, several distinct ice limits associated with the Cockburn Substage are identifiable (e.g., Sam Ford fjord) (17), indicating that the 8.2-ka event glacier response may be superimposed upon a broader pattern of glacier advance

and retreat between  $\sim 9.5$  and  $8$  thousand cal yr B.P. whose climatic importance, if any, remains unclear. Nonetheless, the 8.2-ka event cooling was sufficient to trigger a widespread response of eastern Baffin Island glaciers, perhaps correlative with early Holocene advances of the western Greenland Ice Sheet (18). In addition, the 8.2-ka event triggered an advance of the eastern LIS indicating that ice sheets are capable of an extremely rapid glaciological response (i.e., centennial-scale or less) to a short-lived climate perturbation.

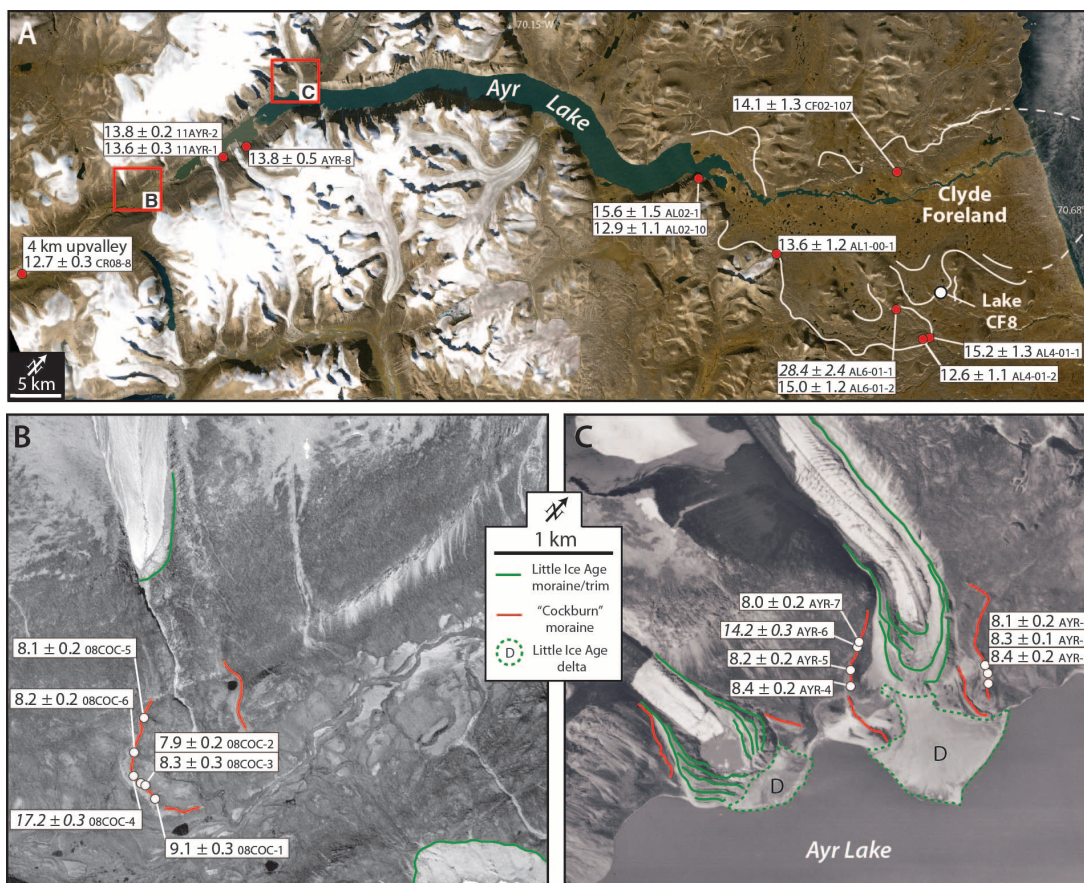
Because the 8.2-ka moraines rest directly on the Ayr Lake valley floor that deglaciated  $\sim 14$  to  $13$  ka, 8.2-ka event moraines mark the most extensive limit of local mountain glaciers since  $\sim 14$  ka. Therefore, our chronology indicates that mountain glaciers were larger during the 8.2-ka event than during the YD. Although our chronology does not preclude a YD-triggered advance of Ayr Lake mountain glaciers, the morphostratigraphic relationship between the 8.2-ka moraines and the Ayr Lake valley floor requires glaciers during the YD to have been less extensive than they were during the 8.2-ka event. The larger response of Baffin Island glaciers to the 8.2-ka event relative to the YD is surprising considering the significantly longer duration and greater amplitude of YD temperature change compared with the 8.2-ka event.

The absence of a distinct YD moraine on Baffin Island is not necessarily unexpected. For

example, unequivocal YD moraines in the Northern Hemisphere have not been identified outside northern Europe, and in the Southern Hemisphere mid-latitudes, glaciers appear to have advanced before, and then retreated during, the YD interval (4, 19). On eastern Greenland, a major moraine complex brackets the YD but, perhaps more importantly, indicates that YD summertime cooling was only  $3.9^\circ$  to  $6.6^\circ\text{C}$  relative to today (7), much less than the  $\sim 15^\circ\text{C}$  mean annual cooling recorded in central Greenland ice cores by gas-fractionation paleothermometry (2).

An independent proxy record from Lake CF8 in our study area indicates that summer temperatures during the 8.2-ka event lowered by  $\sim 3.5^\circ\text{C}$  (20) (Figs. 2 and 3). At high northern latitudes,  $\sim 90\%$  of the variability in glacier mass balance is controlled by ablation-season (summer) temperature (21), and thus summertime cooling of  $\sim 3.5^\circ\text{C}$  during the 8.2-ka event helped drive eastern Baffin Island mountain glaciers to advance beyond their YD limit. Precipitation rates during the YD, however, were up to  $\sim 50$  to  $100\%$  less than early Holocene values (22, 23) and likely contributed to a restricted YD ice extent. Because a  $\sim 40$  to  $50\%$  change in precipitation is equivalent to a  $\sim 1^\circ\text{C}$  temperature change (24, 25), we constrain the magnitude of summer cooling during the YD on eastern Baffin Island to have been no more than  $\sim 4.5^\circ$  to  $5.5^\circ\text{C}$ . This level of summer cooling during the YD is consistent

**Fig. 2.** (A) The Clyde Foreland with recessional ice limits (11) and Ayr Lake valley with  $^{10}\text{Be}$  ages (ka) (1 SD analytical uncertainty) that constrain retreat of the LIS outlet glacier through Ayr Lake valley. (B and C)  $^{10}\text{Be}$  ages from moraine boulders deposited by local mountain glaciers.





with strong seasonality when considering the  $\sim 15^{\circ}\text{C}$  mean annual cooling recorded in Greenland ice cores (6).

In contrast, the  $3.5^{\circ}\text{C}$  of summer cooling recorded on Baffin Island during the 8.2-ka event is indistinguishable from central Greenland mean annual temperatures depicting a peak 8.2-ka temperature depression of  $\sim 3^{\circ}$  to  $4^{\circ}\text{C}$  (26, 27) (Fig. 3). Furthermore, terrestrial proxy records and model simulations of the 8.2-ka event climate [e.g., (3)] typically assert that maximum cooling in the North Atlantic region occurred downstream (east) of the 8.2-ka event's epicenter in the Labrador Sea due to westerly atmospheric and oceanic circulation patterns. Deposition of the Cockburn moraines on Baffin Island, combined with the independent summer temperature reconstruction from the Clyde Foreland, indicates that significant summer cooling during the 8.2-ka event extended west of the Labrador Sea. Unlike YD cooling, cooling during the 8.2-ka event included a significant summer component, and we suggest that the difference in mountain-glacier response between the YD and the 8.2-ka event was due to contrasting seasonality. What remains unclear, however, is the driving mechanism(s) that would allow for the 8.2-ka event to have a proportionally stronger summer-based regional cooling signature than the YD, because both cold reversals are thought to have shared similar reorganizations of North Atlantic thermohaline circulation and concomitant expansion in sea-ice coverage (3, 6, 28).

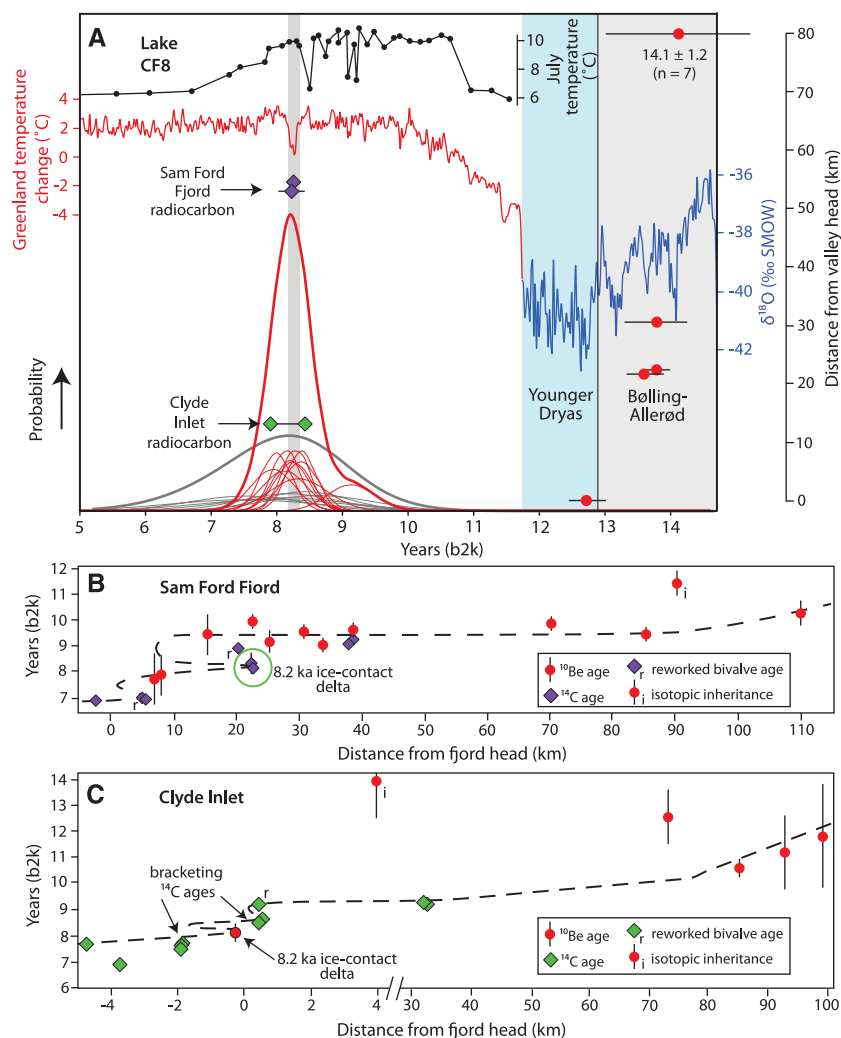
One explanation may involve each cold period's triggering mechanism. The 8.2-ka event is linked to the catastrophic drainage of Laurentide-dammed lakes and routing of meltwater through the Hudson Strait directly into the Labrador Sea (29). Accordingly, the sharp isotopic onset of the 8.2-ka event in Greenland ice cores is consistent with rapid North Atlantic freshening. The origin of the YD, however, remains debated [e.g., (28)]. Although one of several possible YD triggers invokes the sudden release of North American meltwater into the North Atlantic, no geomorphic evidence lending support to this hypothesis has been identified (30), and compared to the 8.2-ka event's onset, the beginning of the YD is less notably abrupt and succeeds a millennial-scale cooling trend (28). It has also been suggested that a Heinrich ice armada outburst (i.e., Heinrich event H0) occurred in Baffin Bay at the onset of the YD (31). However, because multiple Heinrich events occurred through the last glacial period, a Heinrich-related YD triggering mechanism would indicate that the YD is not the product of a one-time catastrophic event (28) but rather the result of a reoccurring pace-maker. Moreover, stalagmite  $\delta^{18}\text{O}$  records suggest that the YD and previous YD-like events are inherent, nonstochastic components of ice-age terminations (32).

Each cold reversal's unique isotopic expression suggests differing causations and possibly different hemispheric climatic imprints. The sud-

den influx of freshwater into the Labrador Sea resulted in significant summer cooling in the Baffin Bay region during the 8.2-ka event, whereas an alternative YD triggering mechanism may have led to comparatively restricted YD summer cooling in Baffin Bay. Indeed, a recent climate model simulation of the 8.2-ka event depicts a strengthened North Atlantic subpolar gyre with maximum sea-surface cooling occurring along the western edge of the gyre (33). Furthermore, an open Nares Strait channeling frigid Arctic waters into the region, and multiple pre-8.2-ka freshwater outbursts into the Labrador Sea, likely resulted in a preconditioned Baffin Bay climate system that crossed a threshold during the 8.2-ka event, resulting in strong regional cooling (34).

Our results provide direct age limits for the Cockburn moraine system deposited by the LIS

and local mountain glaciers and highlight the importance of generating regional records of climate variability spanning intervals of abrupt climate change. The severity of the YD compared with the 8.2-ka event is obvious in central Greenland, yet our results indicate that the latter resulted in more extended Baffin Island mountain glaciers, perhaps due to different triggering mechanisms and unique pre-8.2-ka event climatic baseline conditions in the Baffin Bay region. In addition, the comparatively restricted YD summer cooling on Baffin Island reinforces the broader pattern of mild YD summers in Greenland-proximal locations (5, 7). The amplitude of Baffin Island summer temperature depression during the 8.2-ka event is similar to the drop in Greenland mean annual temperature, indicating a fundamental contrast in seasonality between YD and 8.2-ka event climates.



**Fig. 3.** (A) Ayr Lake valley  $^{10}\text{Be}$  ages plotted as distance from the valley head. The normal kernel density estimate depicts individual and summed  $^{10}\text{Be}$  ages from Ayr Lake moraine boulders (red) and boulders atop the Clyde Inlet ice-contact delta (gray). Results from central Baffin Island are compared to Greenland isotopic (North Greenland Ice Core Project) and elevation-corrected temperature records (27, 36) and to a local summer temperature reconstruction (Lake CF8) (19). (B and C) The full deglaciation histories of Sam Ford fjord and Clyde Inlet (14–16).  $^{14}\text{C}$  ages that directly relate to 8.2-ka ice-contact deltas are highlighted and also presented in (A) (14).



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**Acknowledgments:** We thank M. Badding, D. Bedard, S. McGrane, N. Michelutti, and E. Thomas, who aided in sample collection. We also thank G. Miller for insightful discussions and the helpful comments from two anonymous reviewers. This work was funded in part by U.S. National Science Foundation awards ARC-909334, BCS-1002597, and BCS-752848 to J.P.B.

## Supplementary Materials

www.sciencemag.org/cgi/content/full/337/6100/1330/DC1

Materials and Methods

Figs. S1 to S4

Tables S1 to S3

References (37–55)

2 April 2012; accepted 21 August 2012

10.1126/science.1222759

# Initiation of Cell Wall Pattern by a Rho- and Microtubule-Driven Symmetry Breaking

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A specifically patterned cell wall is a determinant of plant cell shape. Yet, the precise mechanisms that underlie initiation of cell wall patterning remain elusive. By using a reconstitution assay, we revealed that ROPGEF4 (Rho of plant guanine nucleotide exchange factor 4) and ROPGAP3 [ROP guanosine triphosphatase (GTPase)-activating protein 3] mediate local activation of the plant Rho GTPase ROP11 to initiate distinct pattern of secondary cell walls in xylem cells. The activated ROP11 recruits MIDD1 to induce local disassembly of cortical microtubules. Conversely, cortical microtubules eliminate active ROP11 from the plasma membrane through MIDD1. Such a mutual inhibitory interaction between active ROP domains and cortical microtubules establishes the distinct pattern of secondary cell walls. This Rho-based regulatory mechanism shows how plant cells initiate and control cell wall patterns to form various cell shapes.

Cell shape is the basis of behavior and function of specialized cells in multicellular organisms. The plasma membrane plays central roles in the development of the functional and structural polarization of the cell. In plants, plasma membrane polarization leads to the formation of the locally specialized architecture of cell walls, resulting in various shapes of plant cells with specific functions (1–4). However, how local domains in the plasma membrane are formed and how they control local cell wall architecture in conjunction with the cytoskeleton remain a mystery. The plant-specific microtubule

binding protein MIDD1 is anchored to the plasma membrane domains and promotes local microtubule disassembly, forming a specific pattern of secondary walls in xylem vessel cells (5). MIDD1 binds Rho guanosine triphosphatases (GTPases) (6–8), which regulate cell polarization in diverse organisms (1, 9, 10). We found four ROP (Rho of plants) GTPases that were expressed in xylem cells on the basis of a metaxylem vessel-related gene expression database (11). Because of difficulty in direct observation of subcellular localization of these ROPs in developing xylem cells in situ, we observed green fluorescent protein (GFP)-ROPs expressed under the control of an estrogen-inducible system (12) in vitro *Arabidopsis* metaxylem cell culture (5). Only GFP-ROP11 showed colocalization with filamentous structures in secondary wall pits (fig. S1, A to C). Time-lapse observation revealed that GFP-ROP11 accumulated at the end of filaments (fig. S1D), as does MIDD1 (5). Double label-

ing confirmed the colocalization of GFP-ROP11 and tag red fluorescent protein (tagRFP)-MIDD1 (Fig. 1A). In nonxylem cells, which normally lack MIDD1, GFP-ROP11 was localized along a filamentous structure only when MIDD1 was ectopically coexpressed (fig. S2A). Thus, MIDD1 can recruit ROP11 along cortical microtubules. The N-terminal domain of MIDD1 binds to microtubules, and the C-terminal domain of MIDD1 is anchored to the plasma membrane in the secondary wall pits (5). To determine whether ROP11 can recruit MIDD1 to the plasma membrane, we introduced tagRFP-MIDD1<sup>AN</sup> together with GFP-ROP11, a fusion protein of GFP and a constitutive active form of ROP11 (GFP-ROP11<sup>G17V</sup>), or a fusion protein of GFP and a constitutive negative form of ROP11 (GFP-ROP11<sup>T22N</sup>) (13) into nonxylem cultured cells, which normally lack MIDD1. tagRFP-MIDD1<sup>AN</sup> colocalized with GFP-ROP11<sup>G17V</sup> and GFP-ROP11 on the plasma membrane but not with GFP-ROP11<sup>T22N</sup> (fig. S2B). Thus, the GTP-bound form of ROP11 can recruit MIDD1 to the plasma membrane. Introduction of a constitutive active ROP11 (GFP-ROP11<sup>G17V</sup> or GFP-ROP11<sup>Q66L</sup>), but not GFP-ROP11, into differentiating metaxylem cells disrupted the pit-specific localization of MIDD1<sup>AN</sup> such that distribution of MIDD1<sup>AN</sup> became uniform (fig. S3) and secondary walls were formed throughout the cell surface (Fig. 1, B and C). Transgenic *Arabidopsis* plants expressing *LexA* (operator of bacterial repressor)::GFP-ROP11<sup>G17V</sup> or *LexA*::GFP-ROP11<sup>Q66L</sup> also exhibited disorganized secondary walls without obvious pits in metaxylem vessels, although the secondary wall pattern of protoxylem vessels was not visibly affected (fig. S4). A bimolecular fluorescence complementation (BiFC) assay using ROP11 fused with the C-terminal half of yellow fluorescent protein (cYFP-ROP11) and MIDD1<sup>AN</sup> fused with the N-terminal half of YFP (nYFP-MIDD1<sup>AN</sup>) in leaf epidermis revealed that nYFP-MIDD1<sup>AN</sup>

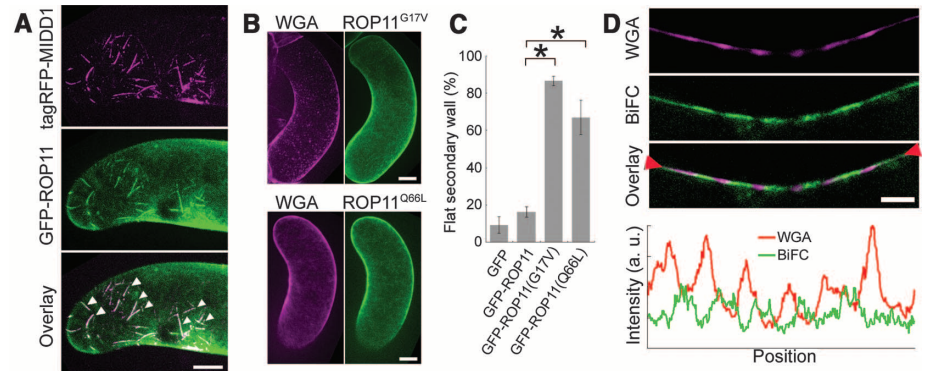
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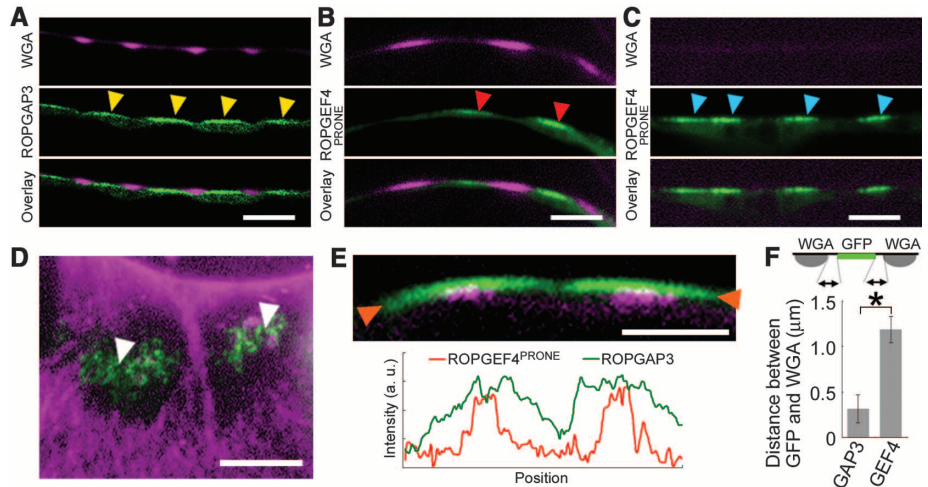
interacted with cYFP-ROP11 or cYFP-ROP11<sup>G17V</sup> but not with cYFP-ROP11<sup>T22N</sup> (fig. S5), suggesting that MIDD1<sup>ΔN</sup> binds only active ROP11. The BiFC assay in differentiating metaxylem cells revealed preferential signals in the secondary wall pits (Fig. 1D). Similarly, fluorescence resonance energy transfer (FRET) between MIDD1<sup>ΔN</sup>-CFP and YFP-ROP11 was detected in the secondary wall pits (fig. S6). These results suggest that ROP11 is present in its GTP-bound form at the plasma membrane beneath the secondary wall pits, where it functions to recruit MIDD1.

ROP activation and inactivation are mediated by ROP guanine nucleotide exchange factor, ROPGEF (14, 15), and ROP GTPase activating protein, ROPGAP (16), respectively. From the metaxylem cell-specific gene expression database (11), we found that ROPGAP3, ROPGAP5, ROPGEF4, and ROPGEF7 are up-regulated during xylem differentiation. We examined the localization of these proteins in differentiating xylem cells with GFP-fusion constructs. Although GFP-ROPGAP3 was localized preferentially at the plasma membrane in the secondary wall pits (Fig. 2A), the other ROPGAPs and ROPGEFs were broadly distributed across the plasma membrane or throughout the cytoplasm (fig. S7, A to C). ROPGEF proteins are composed of a catalytic domain named PRONE and variable regions at either or both of their N or C terminal ends (14, 15). The variable region of a ROPGEF can prevent its PRONE domain from accessing ROPs (17). Therefore, we next examined localization of PRONES of ROPGEF4 and ROPGEF7. GFP-ROPGEF7<sup>PRONE</sup> and GFP-ROPGEF4<sup>PRONE</sup> localized weakly and strongly, respectively, at the plasma membrane in the secondary wall pits (Fig. 2B and fig. S7D). GFP-ROPGEF4<sup>PRONE</sup> accumulated at the plasma membrane in the center region of secondary wall pits as punctuated structures (Fig. 2, D to F). The clustering of GFP-ROPGEF4<sup>PRONE</sup> occurred before the beginning of secondary wall deposition (Fig. 2C). *ROPGEF4* was expressed strongly in metaxylem cell files in *Arabidopsis* roots (fig. S8). Knockdown and knockout of *ROPGEF4* caused reduced density of secondary wall pits in metaxylem vessels (fig. S9). These results suggest that ROPGEF4 plays an essential role in the patterning of pitted secondary wall, probably by local activation of ROPs. In contrast, spiral secondary walls in protoxylem vessels were not affected significantly by knockout of *ROPGEF4* or by expression of constitutive active ROP11.

To understand the relations between ROPGEF4, ROPGAP3, and ROP11, we coexpressed ROP11, GFP-ROPGEF4<sup>PRONE</sup>, and tagRFP-ROPGAP3 under the estrogen-inducible system in the leaf epidermis of *Nicotiana benthamiana*, in which no secondary wall-related active ROP domain exists and active ROP domain formation can be analyzed quantitatively. The coexpression induced GFP-ROPGEF4<sup>PRONE</sup> accumulation as clusters on the plasma membrane, which mimics that in differentiating metaxylem cells (fig. S10A). To examine whether the clusters of ROPGEF4<sup>PRONE</sup>



**Fig. 1.** Active ROP11 is localized in secondary wall pits to anchor MIDD1. (A) tagRFP-MIDD1 and GFP-ROP11 in differentiating xylem cells. Both signals are substantially overlapped (white arrowheads). (B) Secondary wall pattern (WGA) of a cell expressing GFP-ROP11<sup>G17V</sup> or GFP-ROP11<sup>Q66L</sup>. (C) Percentages of cells that developed flat secondary walls without pits. Data are means  $\pm$  SD of three experiments ( $n > 200$  cells),  $*P < 0.01$  [analysis of variance (ANOVA) with Scheffe test]. (D) Confocal cross-sections of cell cortex in a differentiating xylem cell expressing nYFP-ROP11 and cYFP-MIDD1<sup>ΔN</sup>. The intensity plots of BiFC and WGA along the plasma membrane between red arrowheads are shown below the images. Scale bars indicate 5  $\mu$ m; a.u., arbitrary units.



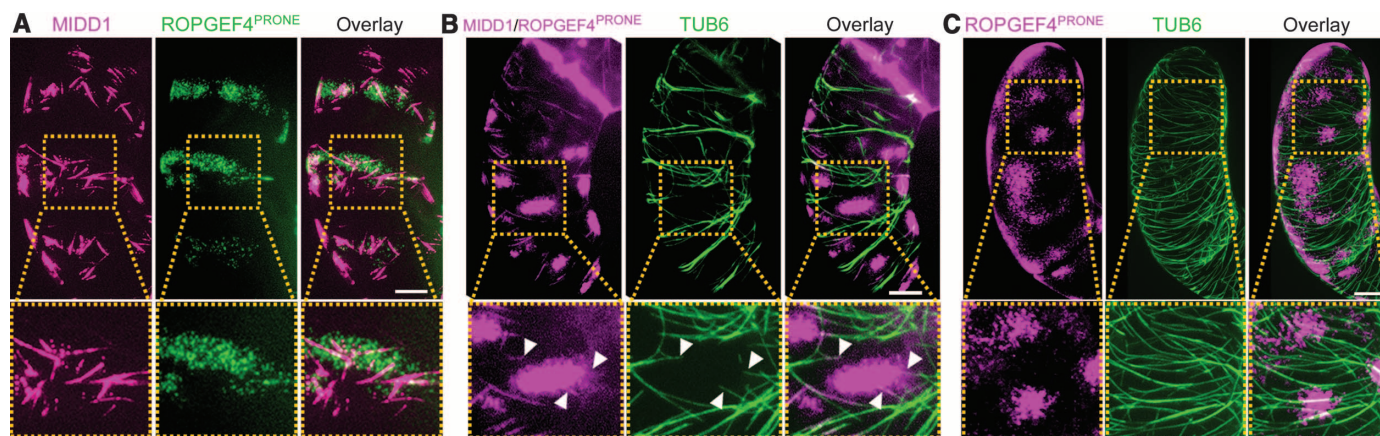
**Fig. 2.** ROPGAP3 and ROPGEF4 localize preferentially in secondary wall pits in differentiating xylem cells. (A and B) Accumulation of GFP-GAP3 [(A), yellow arrowheads] and GFP-ROPGEF4<sup>PRONE</sup> [(B), red arrowheads] at the plasma membrane in the secondary wall pits. (C) Accumulation of GFP-ROPGEF4<sup>PRONE</sup> at the plasma membrane (cyan arrowheads) in early differentiating xylem cells. (D) Accumulation of GFP-ROPGEF4<sup>PRONE</sup> (green) at the center of pits (white arrowheads) of the secondary wall (magenta). (E) Double labeling of GFP-ROPGAP3 (green) and tagRFP-ROPGEF4<sup>PRONE</sup> (magenta) in differentiating xylem cells (top). Intensity profile between the orange arrowheads (bottom). (F) Distance between the edge of GFP signals and WGA signals. Values are means  $\pm$  SD ( $n = 7$  pits),  $*P < 0.01$  ( $t$  test). The location of GFP-ROPGEF4<sup>PRONE</sup> is more central than that of GFP-ROPGAP3. Scale bars, 5  $\mu$ m.

induce local activation of ROP, we introduced tagRFP-MIDD1<sup>ΔN</sup> as a marker labeling active ROPs together with ROP11, ROPGAP3, and GFP-ROPGEF4<sup>PRONE</sup>. tagRFP-MIDD1<sup>ΔN</sup> localized in and around clusters of GFP-ROPGEF4<sup>PRONE</sup> (fig. S10, B and C). Thus, clusters of ROPGEF4<sup>PRONE</sup> induce local activation of ROP11. The clustering of ROPGEF4<sup>PRONE</sup> needed both ROP11 and ROPGAP3 (fig. S11, A and C). Replacing ROP11 with ROP11<sup>G17V</sup> or ROP11<sup>T22N</sup> abolished the clustering of ROPGEF4<sup>PRONE</sup> (fig. S11, B and C). Replacement of these proteins with other family members reduced the frequency of

the GFP-ROPGEF4<sup>PRONE</sup> clustering except for ROPGAP4 (fig. S12, A to C). The replacement of GFP-ROPGEF4<sup>PRONE</sup> with GFP-ROPGEF4 did not cause its clustering (fig. S12D), suggesting the absence of a machinery activating GFP-ROPGEF4 in tobacco epidermal cells. Disruption of microtubules or actin microfilaments did not affect GFP-ROPGEF4<sup>PRONE</sup> clustering (fig. S13). These results indicate that the combination of ROP11, GFP-ROPGEF4<sup>PRONE</sup>, and ROPGAP3 directs clustering of GFP-ROPGEF4<sup>PRONE</sup>.

This spontaneously formed complex can induce MIDD1-dependent local microtubule



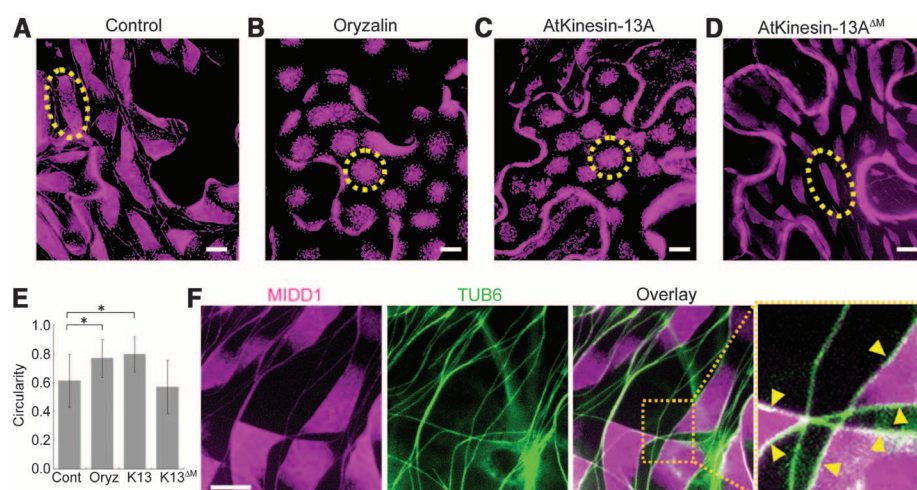


**Fig. 3.** Reconstitution of the active ROP domains and local microtubule disruption in nonxylem cells. **(A to C)** Localization of ROPGEF4<sup>PRONE</sup> and microtubules in nonxylem *Arabidopsis* cultured cells. Areas encircled by yellow dotted lines are magnified below. ROP11 and ROPGAP3 were coexpressed

with tagRFP-MIDD1 and GFP-ROPGEF4<sup>PRONE</sup> (A); tagRFP-MIDD1, tagRFP-ROPGEF4<sup>PRONE</sup>, and GFP-TUB6 (B); or tagRFP-ROPGEF4<sup>PRONE</sup> and GFP-TUB6 (C). Without MIDD1, cortical microtubules are not depolymerized around tagRFP-ROPGEF4<sup>PRONE</sup> clusters (C). Scale bars, 5  $\mu$ m.

disassembly. Leaf epidermal cells had scattered microtubules that were not suitable for this microtubule-disassembly analysis. Therefore, we used nondifferentiating *Arabidopsis* cells in vitro (Fig. 3). We established a stable *LexA::ROP11* cell culture line and then introduced transiently the *LexA::GFP-ROPGEF4<sup>PRONE</sup>/LexA::ROPGAP3* construct. As observed in the tobacco leaf epidermis, coexpression of these proteins resulted in clustering of GFP-ROPGEF4<sup>PRONE</sup> (fig. S14). Coexpression of tagRFP-MIDD1 with the three proteins visualized tagRFP-MIDD1-labeled filamentous structures around the GFP-ROPGEF4<sup>PRONE</sup> clusters (Fig. 3A). Further introduction of a GFP-tubulin gene revealed that the MIDD1-labeled filamentous structures around the clusters of ROPGEF4<sup>PRONE</sup> were depolymerizing microtubules (Fig. 3B, white arrowheads). Without MIDD1, the cortical microtubules were not depolymerized around the clusters of ROPGEF4<sup>PRONE</sup> (Fig. 3C). Thus, the clustering of ROPGEF4<sup>PRONE</sup> produces plasma membrane domains at which MIDD1 is anchored, which in turn cause local microtubule disassembly.

Although we showed that the plasma membrane domains can be produced by spontaneous local activation of ROP11, the cortical microtubules and secondary wall patterning are not fully explained, because secondary wall pits and MIDD1<sup>AN</sup>-labeled domains were more elongated in taxol-treated cells than in nontreated cells (fig. S15). Quantification of fluorescence revealed that taxol treatment enhances the fluorescence of GFP-MIDD1<sup>AN</sup> in the secondary wall pits, whereas oryzalin treatment reduces the fluorescence (fig. S16). These results suggest that cortical microtubules are required to retain MIDD1 in the plasma membrane domains, probably by inhibiting the diffusion of the MIDD1-ROP11 complex. To investigate this idea further, we reconstituted local ROP activation domains by introducing ROP11, GFP-ROPGEF4<sup>PRONE</sup>, ROPGAP3, and tagRFP-MIDD1 into tobacco leaf epidermis,



**Fig. 4.** Cortical microtubules restrict the localization of the active ROP11-MIDD1 complex. **(A to D)** Shape of tagRFP-MIDD1-labeled plasma membrane domains reconstituted in leaf epidermal cells of *N. benthamiana* coexpressing ROPGEF4<sup>PRONE</sup>, ROP11, and ROPGAP3. Yellow dotted circles indicate plasma membrane domains with tagRFP-MIDD1. (A) Treated with mock. (B) Treated with 30  $\mu$ M oryzalin. (C) Coexpressed with AtKinesin-13A. (D) Coexpressed with AtKinesin-13A<sup>ΔM</sup> (inactive form). **(E)** Circularity ( $2\pi \times \text{area/perimeter}^2$ ) of the plasma membrane domains marked with tagRFP-MIDD1 in leaf epidermal cells. Values are means  $\pm$  SD ( $n > 300$  domains), \* $P < 0.01$  (ANOVA with Scheffe test). **(F)** Visualization of cortical microtubules (GFP-TUB6) and plasma membrane domains (tagRFP-MIDD1) in leaf epidermal cells coexpressing ROP11, ROPGAP3, and ROPGEF4<sup>PRONE</sup>. Cortical microtubules run along the borders of the plasma membrane domains (arrowheads). Scale bars, 5  $\mu$ m.

where scattered microtubules allowed clear imaging of the spatial relations between microtubules and ROP activation domains. tagRFP-MIDD1 was located at the plasma membrane in elongated clusters (Fig. 4, A and E). Visualization of cortical microtubules with GFP-TUB6 revealed that the elongated plasma membrane domains were encircled by cortical microtubules that run along the boundary of the plasma membrane domains (Fig. 4F). Disruption of microtubules by oryzalin treatment or transient expression of AtKinesin-13A, whose members are well known to function in microtubule disruption in animals (18), re-

sulted in rounder tagRFP-MIDD1 domains, although inactive AtKinesin-13A did not affect the shape (Fig. 4, B to E). These results indicate that cortical microtubules restrict the localization of the plasma membrane-anchored MIDD1-ROP11 complex. To clarify how cortical microtubules restrict the localization of the MIDD1-ROP11 complex along the plasma membrane, we examined the interaction among YFP-ROP11, cyan fluorescent protein (CFP)-MIDD1<sup>AN</sup>, and tagRFP-TUB6 (microtubules) in tobacco leaf epidermis (fig. S17). ROP11 and MIDD1<sup>AN</sup> were eliminated by the cortical microtubules when the two



proteins were coexpressed (fig. S17B). However, microtubules did not eliminate ROP11 or MIDD1<sup>AN</sup> when ROP11 or MIDD1<sup>AN</sup> was solely expressed (fig. S17, A and C). In contrast, cortical microtubules eliminated MIDD1<sup>AN</sup>-AD, in which a minimal plasma membrane-anchored domain from ROP11 (19) was fused to MIDD1<sup>AN</sup> (fig. S17D). These results suggest that MIDD1 mediates elimination of ROP11 from the plasma membrane by the cortical microtubules, probably by the mechanism in which plasma membrane-associated cortical microtubules physically interfere the plasma membrane-anchored MIDD1-ROP11 complexes.

We show that secondary wall pattern is established by two processes: a ROP-driven symmetry breaking and a mutual inhibitory interaction between cortical microtubules and active ROP domains (fig. S18). The first process may be explained by Turing's reaction diffusion model (20), where ROPGEF4 and ROPGAP3 act as an activator and an inhibitor, respectively. This model requires a positive feedback of the activator. In yeast, a scaffold protein, Bem1p, mediates a positive feedback of Cdc24p GEF (21). A similar scaffold protein might function with ROPGEF4. In the second process, MIDD1 promotes disassembly at the microtubule tip (5), whereas MIDD1 mediates the elimination of active ROPs at the microtubule sides. MIDD1 may interact with AtKinesin-13A (8) as well as ROP11 and cortical microtubules. MIDD1 may have different functions at the tip and side of cortical microtubules.

We showed that MIDD1-mediated interaction between spontaneously activated ROP domains and cortical microtubules produces pitted pattern

of metaxylem cells. Although *ropgef4* did not affect significantly protoxylem cell wall patterns, because not only MIDD1 but also members of ROPs are also expressed in protoxylem cells (22), such secondary wall patterns as annular, spiral, and reticulate patterns might be produced by similar MIDD1-mediated interaction between activated ROP domains and cortical microtubules. Indeed, stabilization of microtubules with taxol produced a reticulate-like secondary wall pattern in developing metaxylem cells. Differences among ROPGEF and/or ROPGAP members may also contribute to size differences of activated ROP domains and then of the secondary wall depleted area. Our reconstitution assay may be a powerful tool to test this idea.

MIDD1 is expressed in not only xylem cells but also nonxylem cells (23). Considering the nature of MIDD1, even in nonxylem cells, MIDD1 may function in production of specific patterns of cortical microtubules and of activated ROP domains. As shown in epidermal pavement cells, local ROP domain activation and microtubule organization underlie local polarized growth of the cell (1). Thus, MIDD1-mediated membrane domain establishment may contribute to the formation of various plant cell shapes generally.

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**Acknowledgments:** We thank N. Chua of the Rockefeller University for providing the pER8 vector; U. Grossniklaus of the University of Zurich for providing the pMDC7 vector; T. Nakagawa of Shimane University for providing the pGWB vectors; Y. Ohya of the University of Tokyo for critical reading of this manuscript; A. Nakano, T. Ueda, and S. Betsuyaku of the University of Tokyo for technical advice; and Y. Nakashima for technical assistance. This work was supported partly by Grants-in-Aid from the Ministry of Education, Science, Sports and Culture of Japan (19060009) to H.F.; from the Japan Society for the Promotion of Science to H.F. (23227001) and Y.O. (22870005) and the NC-CARP project; and from JST, Precursory Research for Embryonic Science and Technology (PRESTO) to Y.O. (20103).

#### Supplementary Materials

www.sciencemag.org/cgi/content/full/337/6100/1333/DC1  
Materials and Methods  
Figs. S1 to S18  
Table S1  
References (24, 25)

29 March 2012; accepted 9 July 2012  
10.1126/science.1222597

## A Killer-Protector System Regulates Both Hybrid Sterility and Segregation Distortion in Rice

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Hybrid sterility is a major form of postzygotic reproductive isolation that restricts gene flow between populations. Cultivated rice (*Oryza sativa* L.) consists of two subspecies, *indica* and *japonica*; inter-subspecific hybrids are usually sterile. We show that a killer-protector system at the *S5* locus encoded by three tightly linked genes [*Open Reading Frame 3* (*ORF3*) to *ORF5*] regulates fertility in *indica-japonica* hybrids. During female sporogenesis, the action of *ORF5*+ (killer) and *ORF4*+ (partner) causes endoplasmic reticulum (ER) stress. *ORF3*+ (protector) prevents ER stress and produces normal gametes, but *ORF3*− cannot prevent ER stress, resulting in premature programmed cell death and leads to embryo-sac abortion. Preferential transmission of *ORF3*+ gametes results in segregation distortion in the progeny. These results add to our understanding of differences between *indica* and *japonica* rice and may aid in rice genetic improvement.

**R**eproductive isolation is both an indicator of speciation and a mechanism for maintaining species identity. The Dobzhansky-

Muller model (1) suggests that hybrid incompatibility results from deleterious interactions between independently evolved loci from diverged populations.

Studies in animal models such as *Drosophila* and mice have identified several of such interactive genes that cause hybrid incompatibility and segregation distortion (2, 3). In plants, hybrid sterility is a major form of postzygotic reproductive isolation, and several genes have been identified that conform to the Dobzhansky-Muller model for reproductive isolation (4–7). Hybrid sterility between *indica* and *japonica* subspecies of cultivated rice (*Oryza sativa* L.) is one example of postzygotic reproductive isolation in plants (8–10). Genetic analyses of *indica-japonica* hybrids have identified a large number of loci conditioning hybrid sterility (10). Several genes for *indica-japonica* hybrid sterility (11–13) and interspecific hybrid sterility between *O. sativa* and *O. glumaepatula* (14) were recently cloned, aiding in our understanding of the biological processes of hybrid sterility in rice species.

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*S5* is a major locus for hybrid sterility in rice that affects embryo-sac fertility, as identified in a number of studies across a range of germplasms (11, 15–19). The *S5* locus has three alleles, an *indica* allele *S5-i*, a *japonica* allele *S5-j*, and a neutral allele *S5-n* (15). Hybrids of genotype *S5-i/S5-j* are mostly sterile, whereas hybrids of genotypes consisting of *S5-n* with either *S5-i* or *S5-j* are mostly fertile (15–17). The *S5* region has been mapped (18) and covers up to five open reading frames (*ORF1* to *ORF5*). Transformation studies of *ORF3* to *ORF5* (11) from an *indica* variety into a *japonica* variety showed reduced fertility, due to embryo-sac abortion, for transformants harboring *indica ORF5*, whereas the fertility of transformants of *ORF3* and *ORF4* was not affected. The *indica* and *japonica* alleles of *ORF5*, which encodes an aspartic protease, differ by two nucleotides, whereas the wide compatibility allele has a large deletion in the N terminus of the predicted protein, causing subcellular mislocalization of the protein (11).

Because segregation distortion has been observed in progenies of *indica-japonica* hybrids (12, 19, 20), we assayed *S5* genotypes of 195 seedlings from a BC<sub>2</sub>F<sub>1</sub> plant BL(BL/NJ), a near isogenic line (NIL) heterozygous for the *S5-i* allele from an *indica* variety Nanjing 11, backcrossing successively with a *japonica*-variety Balilla. The resulting progeny showed genotypes deviating from the expected 1:2:1 ratio (Table 1). A maximum likelihood estimate for the frequency of *S5-j* transmitted via the female gametes was 0.1, compared with the expected 0.5. Similar segregation distortion was also observed in

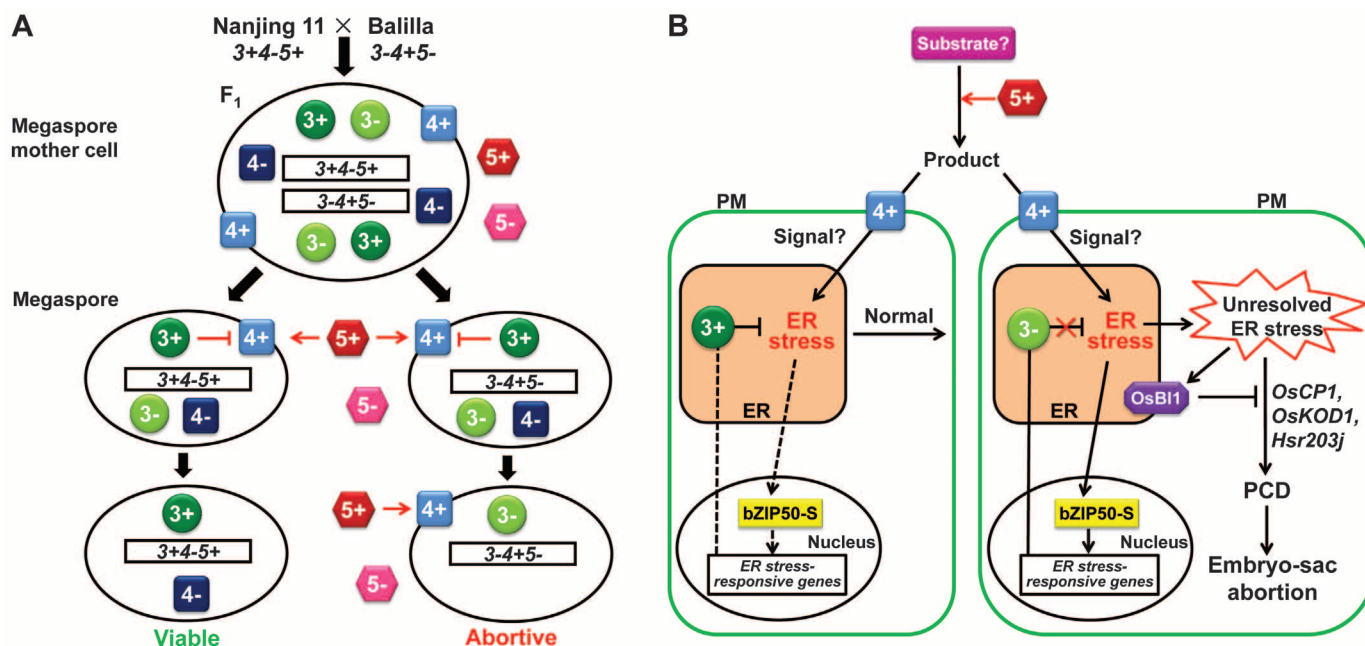
progenies from other *indica-japonica* crosses (Table 1).

Because it is difficult to explain the hybrid sterility and segregation distortion by *ORF5* alone, we determined genomic sequences of *ORF1* to *ORF4* for Nanjing 11 (*indica*), Balilla (*japonica*), Dular, and 02428 (the latter two are wide compatibility varieties that can produce highly fertile hybrids in crosses with either *indica* or *japonica*). Sequence polymorphisms with predictable functional changes among the genotypes in the predicted proteins were observed in *ORF3* and *ORF4* but not *ORF1* or *ORF2* (fig. S1). By investigating the transcripts, we observed that the translation start codons of *ORF4* and *ORF5* were located only 0.8 kb away, but the genes were transcribed in opposite directions. The *ORF4* sequence of Balilla and 02428 was predicted to encode a protein with a transmembrane domain and had no homology with any known proteins (fig. S2). An 11–base pair (bp) deletion predicted to cause premature termination of the predicted protein and a loss of the putative transmembrane domain (fig. S2) was detected in *ORF4* of Nanjing 11 and Dular relative to Balilla and 02428 (fig. S1). *ORF3* was mapped 11.7 kb away from *ORF4* and showed homology to a heat shock protein Hsp70 gene. The *ORF3* sequences of Balilla and Dular have a 13-bp deletion relative to the other two genotypes (fig. S1), which results in a frameshift in the C terminus of the protein (fig. S3). On the basis of the sequence differences in these ORFs (fig. S1), we designated the *ORF3* allele from Nanjing 11 and 02428 as *ORF3+* and the other allele as *ORF3-*; the *ORF4* allele from

Balilla and 02428 as *ORF4+* and the other one as *ORF4-*; and the *ORF5* allele from Nanjing 11 as *ORF5+*, the one from Balilla as *ORF5-*, and those from Dular and 02428 as *ORF5n*.

We tested the effect of *ORF3* on hybrid sterility by crossing a transgenic Balilla*ORF3+* plant [in which *ORF3+* from Nanjing 11 was transformed into Balilla and showing normal fertility (Table 2)] with BL(NJ/NJ), a NIL in which the *S5* fragment contains *ORF3* to *ORF5* from Nanjing 11 (*ORF3+*, *ORF4-*, and *ORF5+*) introgressed into a Balilla background (*ORF3-*, *ORF4+*, and *ORF5-*). A Balilla and BL(NJ/NJ) cross typically produces hybrid with reduced fertility (Table 1). However, BL/NJ*ORF3+* plants from this cross showed 71.5% spikelet fertility, compared with 50.3% of the BL/NJ plants (Table 2). This rescue was confirmed in the progeny of heterozygous plants BL/NJ*ORF3+*, in which the fertility of BL/NJ*ORF3+* plants (75.1%) was much higher than that of BL/NJ plants (46.8%). Therefore, we inferred that *ORF3+* rescued fertility of the *indica-japonica* hybrid, presumably by protecting the gametes from the killing effect of *ORF5+*. Comparison between normal and *ORF3+*-rescued plants [BL/BL or NJ/NJ versus BL/NJ*ORF3+* (Table 2)] showed that the fertility-protecting effect of *ORF3+* is only partial. We suspect that the independent transmission of the transformed hemizygous *ORF3+* relative to the host *S5* locus explains these observations because we would expect only approximately half of the gametes to inherit the *ORF3+* transgene, which would be protected from killing by *ORF5+*.

To support our hypothesis, we crossed Balilla*ORF3+* carrying a transformed *ORF3+*



**Fig. 1.** Schematic representation of the killer-protector system in an *indica-japonica* hybrid regulated by the *S5* locus. **(A)** A genetic model depicting the process of megaspore formation and effects of the three genes, where 3+, 3-, 4+, 4-, 5+, and 5- represent *ORF3+*, *ORF3-*, *ORF4+*, *ORF4-*, *ORF5+*, and *ORF5-*, respectively, and colored blocks and circles represent the proteins. In

the megaspore mother cell and daughter cells immediately after meiotic division, killing would not occur because of the presence of *ORF3+*. Killing would occur in the daughter cell carrying *ORF3-* and *ORF4+* at a later stage of megaspore development. **(B)** Hypothetical molecular processes involving ER-stress and PCD. bZIP50-S, spliced bZIP50; ER, endoplasmic reticulum; PM, plasma membrane.

and Balilla*ORF5*<sup>+</sup> carrying a transformed *ORF5*<sup>+</sup> (Table 2). The progeny plants lacking any transgene were fully fertile, as expected, as were the ones carrying *ORF3*<sup>+</sup> alone. Transgenic *ORF5*<sup>+</sup> plants were sterile, whereas the addition of transgene *ORF3*<sup>+</sup> rescued the fertility of the plants.

Transforming *ORF4*<sup>+</sup> into BL(NJ/NJ) resulted in no fertility reduction in BL(NJ/NJ)*ORF4*<sup>+</sup> transformants (Table 3), as expected, because of the presence of the protector *ORF3*<sup>+</sup> in the introgressed fragment. Also, the fertility of hybrids involving the Dular fragment (*ORF3*<sup>−</sup>, *ORF4*<sup>−</sup>, and *ORF5n*) from the BL(BL/DL) × BL(BL/NJ) cross was normal, regardless of whether the allelic fragment was *indica* or *japonica* (Table 3). However, in the F<sub>1</sub> progeny from a BL(NJ/NJ)*ORF4*<sup>+</sup> × BL(DL/DL) cross, individuals with the transgene BL(DL/NJ)*ORF4*<sup>+</sup> exhibited reduced spikelet fertility (39.3%), compared with the transgene-negative plants BL(DL/NJ) or the parental BL(NJ/NJ)*ORF4*<sup>+</sup>. Furthermore, statistically significant segregation distortion at the *S5* locus was observed in the F<sub>2</sub> progeny produced from BL(DL/NJ)*ORF4*<sup>+</sup> plants (Table 3), in which the NJ fragment (estimated frequency 0.654) was favored at the cost of the DL fragment (0.346). Consequently, the frequency of DL/DL homozygote was deficient compared with the expected 1:2:1 ratio. Thus, the addition of *ORF4*<sup>+</sup> in this hybrid resulted in the death of gametes with the Dular fragment.

To examine the role of *ORF4*<sup>+</sup> in relation to *ORF5*<sup>+</sup>, we crossed BL(BL/DL) with Balilla*ORF5*<sup>+</sup> (Table 3). Among F<sub>1</sub>, the two genotypes with the transformed *ORF5*<sup>+</sup> (BL/B*ORF5*<sup>+</sup> and BL/D*ORF5*<sup>+</sup>) were mostly sterile, whereas their transgene-negative counterparts were fertile. This was also observed in the F<sub>2</sub> segregants of this cross. Moreover, DL/D*ORF5*<sup>+</sup>, which is homozygous for the Dular genotype with an added *ORF5*<sup>+</sup>, showed normal fertility, and fertility of BL(BL/NJ) was not affected by the transformed *ORF5*<sup>+</sup>. Given that both Balilla and Dular had *ORF3*<sup>−</sup> and nonkiller *ORF5*, the fertility difference between BL/D*ORF5*<sup>+</sup> and DL/D*ORF5*<sup>+</sup> can be ascribed to differences in *ORF4* between Balilla and Dular (figs. S1 and S2). Because both *ORF5*<sup>+</sup> and *ORF4*<sup>+</sup> are indispensable for gamete killing, *ORF4* is apparently a partner in gamete killing with *ORF5*.

The results of genetic analysis for the *S5*-induced hybrid sterility presented above are schematically summarized in Fig. 1A. Female gametes in the *indica-japonica* hybrid are killed during sporogenesis by *ORF5*<sup>+</sup> in partner with *ORF4*<sup>+</sup> but protected by *ORF3*<sup>+</sup>.

An expression database (21) indicated that both *ORF4* and *ORF5* show low expression—almost at the background level throughout the life cycle (fig. S4). *ORF3* transcripts were more abundant, especially in developing panicles. Transient expression assays with rice protoplasts revealed that both *ORF3*<sup>+</sup> and *ORF3*<sup>−</sup> proteins localized to the endoplasmic reticulum (ER) (fig. S5, A to H). *ORF4*<sup>+</sup> localized to the plasma membrane and Golgi (fig. S5, Q to T), whereas *ORF4*<sup>−</sup>

localized to the ER (fig. S5, I to P). *ORF5* protein was found in the extracellular domain (11).

Microarray analysis of ovaries at the functional megaspore stage showed that *ORF3* expression was statistically significantly higher in Balilla*ORF5*<sup>+</sup> transgene-positive than in -negative plants (table S1). We detected an ER stress-responsive UPRE-like *cis*-element (TGACGAGG) (22) in the promoter of *ORF3* at −256 bp (fig. S1). Expression of a number of ER stress-responsive genes was also statistically significantly higher in Balilla*ORF5*<sup>+</sup> plants (table S1 and fig. S6A). This pattern of induction is highly similar to that observed in ER stress studies in rice (23–25). As a response to stress (25), the ER stress sensor IRE1 transduces signals through the unconventional splicing of *OsbZIP50* mRNA, which causes a frameshift producing a nuclear localization signal in the protein designated OsbZIP50-S, which regulates the expression of many ER stress-responsive genes, including *ORF3*. We confirmed that the spliced *OsbZIP50-S* mRNA was present in Balilla*ORF5*<sup>+</sup> plants (fig. S7).

Taken together, these results suggested that introduction of *ORF5*<sup>+</sup> into Balilla induced ER-stress in ovaries.

Bax inhibitor-1 (BI1) is a conserved ER-resident cell death suppressor in eukaryotes and plays an important role in modulating the ER stress-mediated programmed cell death (PCD) pathway both in *Arabidopsis* and rice (26, 27). Our analysis (fig. S6B) showed that *OsBI1* was up-regulated in Balilla*ORF5*<sup>+</sup> plants. *OsKOD1* [an orthologous gene of kiss of death (KOD), which acts as a PCD-inducer in *Arabidopsis*] (28) and *Hsr203j* (the commonly used cell death marker) (24, 29) were also up-regulated by *ORF5*<sup>+</sup>. Expression of *OsCPI1*, which acts as an executor of the PCD process in rice tapetum development (30, 31), was elevated by ~12-fold in ovaries of Balilla*ORF5*<sup>+</sup> plants. In addition, many differentially expressed genes between Balilla*ORF5*<sup>+</sup> transgene-positive and -negative plants revealed in the microarrays (table S2) were PCD-related, such as the cytochrome *P450*, *LTP1*, and *GDSL*

**Table 1.** Segregation distortion at the *S5* locus detected in F<sub>2</sub> seedlings from various crosses.

| Population (or cross)  | Generation                     | <i>S5</i> genotype | Number of plants* | $\chi^2$ (1:2:1)         | Spikelet fertility (%)†        |
|------------------------|--------------------------------|--------------------|-------------------|--------------------------|--------------------------------|
| BL(BL/NJ)‡             | BC <sub>6</sub> F <sub>2</sub> | BL/BL              | 9 (48.75)         | 59.5 ( <i>P</i> = 0.00)  | 85.6 ± 2.5 ( <i>P</i> = 0.00)§ |
|                        |                                | BL/NJ              | 101 (97.5)        |                          | 52.6 ± 0.6                     |
|                        |                                | NJ/NJ              | 85 (48.75)        |                          | 89.5 ± 0.9                     |
| Nanjing 11 /Balilla    | F <sub>2</sub>                 | BL/BL              | 10 (46)           | 106.6 ( <i>P</i> = 0.00) |                                |
|                        |                                | BL/NJ              | 70 (92)           |                          |                                |
|                        |                                | NJ/NJ              | 104 (46)          |                          |                                |
| Nanjing 11 /Nipponbare | F <sub>2</sub>                 | NP/NP              | 11 (49.75)        | 80.1 ( <i>P</i> = 0.00)  |                                |
|                        |                                | NP/NJ              | 89 (99.5)         |                          |                                |
|                        |                                | NJ/NJ              | 99 (49.75)        |                          |                                |
| 93-11 /Nipponbare      | F <sub>2</sub>                 | NP/NP              | 18 (53.5)         | 65.1 ( <i>P</i> = 0.00)  |                                |
|                        |                                | 93/NP              | 96 (107)          |                          |                                |
|                        |                                | 93/93              | 100 (53.5)        |                          |                                |

\*Numbers in parentheses are expectations based on 1:2:1 ratio for each cross. †Mean ± SEM. ‡Near isogenic line heterozygous for the *S5* fragment developed by crossing Balilla with Nanjing 11 and backcrossed six times with Balilla. BL, Balilla; NP, Nipponbare; NJ, Nanjing 11; 93, 93-11. §*P* value from a *t* test of the heterozygote against the two homozygotes.

**Table 2.** The effects of *ORF3* and *ORF5* on spikelet fertility.

| Line or cross*                                                      | Generation     | <i>S5</i> genotype†                                    | Number of plants | Spikelet fertility (%)‡ | <i>P</i> value§ |
|---------------------------------------------------------------------|----------------|--------------------------------------------------------|------------------|-------------------------|-----------------|
| Balilla <i>ORF3</i> <sup>+</sup>                                    | T <sub>1</sub> | BL/BL                                                  | 27               | 85.6 ± 1.2              | 0.37            |
|                                                                     |                | BL/B <i>ORF3</i> <sup>+</sup>                          | 30               | 87.1 ± 0.8              |                 |
| BL(NJ/NJ) × Balilla <i>ORF3</i> <sup>+</sup>                        | F <sub>1</sub> | BL/NJ                                                  | 23               | 50.3 ± 0.6              | 0.00            |
|                                                                     |                | BL/NJ <i>ORF3</i> <sup>+</sup>                         | 53               | 71.5 ± 0.6              |                 |
|                                                                     |                | BL(BL/NJ) <i>ORF3</i> <sup>+</sup>                     | 4                | 91.0 ± 3.4              |                 |
| BL(BL/NJ) <i>ORF3</i> <sup>+</sup>                                  | F <sub>2</sub> | BL/BL                                                  | 4                | 91.0 ± 3.4              | 0.00            |
|                                                                     |                | BL/NJ                                                  | 5                | 46.8 ± 0.4              |                 |
|                                                                     |                | NJ/NJ                                                  | 6                | 87.5 ± 0.7              |                 |
|                                                                     |                | BL/B <i>ORF3</i> <sup>+</sup>                          | 10               | 92.7 ± 1.5              |                 |
|                                                                     |                | BL/NJ <i>ORF3</i> <sup>+</sup>                         | 19               | 75.1 ± 1.7              |                 |
|                                                                     |                | NJ/NJ <i>ORF3</i> <sup>+</sup>                         | 15               | 86.6 ± 1.6              |                 |
|                                                                     |                | BL/BL                                                  | 3                | 80.8 ± 0.7              |                 |
| Balilla <i>ORF3</i> <sup>+</sup> × Balilla <i>ORF5</i> <sup>+</sup> | F <sub>1</sub> | BL/B <i>ORF3</i> <sup>+</sup>                          | 5                | 82.7 ± 4.4              | 0.00            |
|                                                                     |                | BL/B <i>ORF5</i> <sup>+</sup>                          | 7                | 3.9 ± 0.8               |                 |
|                                                                     |                | BL/B <i>ORF3</i> <sup>+</sup> <i>ORF5</i> <sup>+</sup> | 13               | 47.7 ± 2.7              |                 |
|                                                                     |                |                                                        |                  |                         |                 |

\*BL(NJ/NJ) and BL(BL/NJ) indicate near-isogenic lines in Balilla background with the *S5* locus homozygous for the fragment from NJ (Nanjing 11), or heterozygous for NJ and BL (Balilla) fragments. †BL, Balilla; NJ, Nanjing 11. ‡Mean ± SEM. §*P* value obtained by *t* test between the two genotypes in the same cross or selected genotypes in the same shade.



gene families (31). These results suggested that ORF5+-induced ER stress might provoke abnormal PCD in embryo-sac development. We performed a terminal deoxynucleotidyl transferase-mediated deoxy-uridine 5'-triphosphate (dUTP) nick-end labeling (TUNEL) assay for PCD by detecting DNA fragmentation during female sporogenesis (fig. S8). No cellular abnormality or TUNEL signal was observed before meiosis (fig. S8, A and B). Cellular abnormality was observed in megasporocyte undergoing meiosis and afterward in BalillaORF5+ (fig. S8, C to J). TUNEL signal occurred earlier and stronger in BalillaORF5+ than in Balilla (fig. S8, C to J). Thus, premature PCD occurred during female sporogenesis in BalillaORF5+, resulting in embryo-sac abortion. In contrast, introduction of ORF3+ into BalillaORF5+ plant by crossing BalillaORF5+ with homozygous BalillaORF3+ restored normal expression levels of the ER stress-responsive and PCD-related genes in the hybrid (fig. S9). This implies that ORF3+ is a suppressor of ORF5+-induced ER stress and subsequent PCD.

On the basis of these results, we hypothesize (Fig. 1B) that the activity of extracellular ORF5+ produces a molecule that is sensed by plasma membrane-localized ORF4+ and eventually triggers ER stress. The ER stress subsequently activates the IRE1-mediated splicing of *OsbZIP50* mRNA, producing OsbZIP50-S, a transcription fac-

tor that turns on expression of ER stress-responsive genes, including *ORF3*. The ER stress is resolved in the presence of ORF3+, thus producing normal female gametes. Whereas in the absence of ORF3+, unresolved ER stress induces PCD-related genes, causing anomalous PCD, which leads to embryo-sac abortion, despite the presence of OsB11. Thus, proteins encoded by *ORF3*, *ORF4*, and *ORF5* are elements involved in different stages of the ER stress-induced PCD pathway regulating hybrid fertility.

We obtained sequences of *ORF3*, *ORF4*, and *ORF5* for 82 accessions of *O. sativa*, *O. rufipogon*, and *O. nivara* from 16 countries over a diverse geographical area (table S3). Nineteen haplotypes were identified containing single-nucleotide polymorphisms (SNPs) and insertions/deletions (Indels) in the coding sequence of *ORF3* (fig. S10). Four of the haplotypes could be placed in the *ORF3*-allele group, and 15 classified into the *ORF3*+ allele group. Five of the 18 haplotypes detected for *ORF4* were classified into the *ORF4*- group and 13 into the *ORF4*+ group. Together with the three allelic groups identified in *ORF5* (*ORF5*+, *ORF5*-, and *ORF5n*) (32), there are a total of 12 possible combinations formed of the three genes. We observed 9 of the 12 combinations (table S4). *ORF3*+, *ORF4*+, and *ORF5*+ was the most common, especially in the two wild rice species *O. rufipogon* and *O. nivara*. This represents a balance between killing and protecting the gametes,

according to our genetic model. The sequence of the outgroup *O. glumaepatula* suggested that *ORF3*+, *ORF4*+, and *ORF5*+ is the ancestral type. The suicidal combination of *ORF3*-, *ORF4*+, and *ORF5*+, which would not be able to survive in nature, was not observed in the sample, although it would be the easiest to be generated at the population level through mutation and/or recombination. Two other combinations (*ORF3*-, *ORF4*-, and *ORF5*+ and *ORF3*-, *ORF4*-, and *ORF5*-) were not detected because of either their rarity or the source of sample. This result was congruent to the proposed genetic model of the killing-protecting system. The typical *indica*-like (*ORF3*+, *ORF4*-, and *ORF5*+) and *japonica*-like (*ORF3*-, *ORF4*+, and *ORF5*-) types were found in wild rice accessions, suggesting that the ancestors of *indica* and *japonica* rice probably originated before domestication. Because *indica* and *japonica* rice (also *indica*-like and *japonica*-like wild rice) have distinct ranges of distribution worldwide, geographical isolation might have played an important role in maintaining distinctions of the rice groups as well as the killer-protector system. This killer-protector system may have a profound implication in the evolution and diversification of rice. Reproductive isolation enforced by the killer (*ORF4*+, *ORF5*+) would have promoted genetic differentiation between *indica* and *japonica* rice, which appears to be a major source of genetic diversity in the rice gene pool, whereas the protector (*ORF3*+) and nonkiller combinations of *ORF4* and *ORF5* would allow for hybridization and gene flow, thus providing a coherent force at the species level.

**Table 3.** The effects of *ORF4* and *ORF5* on spikelet fertility and segregation distortion.

| Line or cross              | Generation     | S5 genotype | Number of plants | Spikelet fertility (%)* | P value |
|----------------------------|----------------|-------------|------------------|-------------------------|---------|
| BL(NJ/NJ)ORF4+             | T <sub>1</sub> | NJ/NJ       | 24               | 87.0 ± 0.7              | 0.31†   |
|                            |                | NJ/NJORF4+  | 26               | 89.3 ± 1.3              |         |
| BL(BL/DL) × BL(BL/NJ)      | F <sub>1</sub> | BL/BL       | 19               | 84.7 ± 0.9              | 0.00‡   |
|                            |                | BL/DL       | 16               | 86.0 ± 1.1              |         |
|                            |                | BL/NJ       | 20               | 51.4 ± 1.0              |         |
|                            |                | DL/NJ       | 23               | 81.8 ± 1.5              |         |
| BL(NJ/NJ)ORF4+ × BL(DL/DL) | F <sub>1</sub> | DL/NJ       | 22               | 79.1 ± 2.6              | 0.00†   |
|                            |                | DL/NJORF4+  | 28               | 39.3 ± 1.9              |         |
| BL(DL/NJ)ORF4+             | F <sub>2</sub> | DL/DL       | 5 (19.5)§        |                         | 0.00§   |
|                            |                | DL/NJ       | 44 (39)          |                         |         |
|                            |                | NJ/NJ       | 29 (19.5)        |                         |         |
| BalillaORF5+               | T <sub>2</sub> | BL/BL       | 8                | 86.9 ± 1.7              |         |
|                            |                | BL/BLORF5+  | 22               | 0.01 ± 0.3              |         |
| BL(BL/DL) × BalillaORF5+   | F <sub>1</sub> | BL/BL       | 10               | 90.7 ± 1.2              |         |
|                            |                | BL/DL       | 10               | 88.8 ± 0.6              | 0.00    |
|                            |                | BL/BLORF5+  | 12               | 1.0 ± 0.2               |         |
|                            |                | BL/DLORF5+  | 24               | 5.9 ± 0.9               |         |
| BL(BL/DL)ORF5+             | F <sub>2</sub> | BL/BL       | 4                | 91.8 ± 3.7              |         |
| from:                      |                | BL/DL       | 7                | 90.9 ± 1.8              | 0.00    |
| BL(BL/DL) × BalillaORF5+   |                | DL/DL       | 2                | 90.9 ± 1.8              |         |
|                            |                | BL/BLORF5+  | 16               | 0.7 ± 0.3               |         |
|                            |                | BL/DLORF5+  | 16               | 3.0 ± 1.1               |         |
|                            |                | DL/DLORF5+  | 9                | 90.6 ± 1.3              |         |
| BL(NJ/NJ) × BalillaORF5+   | F <sub>1</sub> | BL/NJ       | 14               | 52.6 ± 0.4              | 0.51†   |
|                            |                | BL/NJORF5+  | 17               | 52.2 ± 0.5              |         |

\*Mean ± SEM. †Probability obtained from a *t* test between the two genotypes of the same cross. ‡Probability obtained from a *t* test of BL/NJ genotype against the other three genotypes in the same cross. §Probability obtained from a  $\chi^2$  test; expected numbers based on 1:2:1 ratio are in parentheses. ||Probability obtained from a *t* test between the shaded genotypes in the same cross. BL, Balilla; DL, Dular; NJ, Nanjing 11.

## References and Notes

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**Acknowledgments:** We thank D. S. Brar of the International Rice Research Institute for providing the rice seeds, and S. Luan of University of California, Berkeley, USA for discussion. This research was supported by grants from the National Natural Science Foundation (31130032 and 30921091), the 863 Project (2012AA100103), and the 111 Project (B07041) of China. All of the DNA sequences obtained

in this study have been deposited in the GenBank from accession codes JX138498 to JX138505. A patent for the ORF5 sequence has been approved by the State Intellectual Property Office of China (ZL200710053552.9).

#### Supplementary Materials

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23 April 2012; accepted 13 June 2012  
10.1126/science.1223702

# Single Reconstituted Neuronal SNARE Complexes Zipper in Three Distinct Stages

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Soluble *N*-ethylmaleimide-sensitive factor attachment protein receptor (SNARE) proteins drive membrane fusion by assembling into a four-helix bundle in a zippering process. Here, we used optical tweezers to observe in a cell-free reconstitution experiment in real time a long-sought SNARE assembly intermediate in which only the membrane-distal amino-terminal half of the bundle is assembled. Our findings support the zippering hypothesis, but suggest that zippering proceeds through three sequential binary switches, not continuously, in the amino- and carboxyl-terminal halves of the bundle and the linker domain. The half-zipper intermediate was stabilized by externally applied force that mimicked the repulsion between apposed membranes being forced to fuse. This intermediate then rapidly and forcefully zippered, delivering free energy of  $36 k_B T$  (where  $k_B$  is Boltzmann's constant and  $T$  is temperature) to mediate fusion.

**S**oluble *N*-ethylmaleimide-sensitive factor attachment protein receptor (SNARE) proteins mediate membrane fusion in the cell, and in particular the fusion of vesicles stored at nerve endings to release neurotransmitters for synaptic transmission (1, 2). The neuronal SNAREs consist of vesicle-associated membrane protein 2 (VAMP2, also called synaptobrevin) on the vesicle membrane (v-SNARE) and the binary complex of syntaxin 1 and SNAP-25 on the plasma membrane (target or t-SNARE) (3, 4). Together these SNAREs drive membrane fusion by joining into a parallel four-helix bundle (4), which is envisioned to zipper progressively toward the membranes (5), providing force that overcomes an estimated energy barrier of  $>40 k_B T$  (where  $k_B$  is Boltzmann's constant and  $T$  is temperature) (6). Considerable indirect evidence favors the zippering hypothesis (7–12), but direct observation of the assembly intermediates and accurate characterization of the zippering energy and kinetics have been lacking.

We developed a single-molecule manipulation assay to investigate SNARE assembly based

on high-resolution dual-trap optical tweezers (Fig. 1A). We cross-linked the N termini of syntaxin and VAMP2 by a disulfide bridge and attached syntaxin by its C terminus to one bead and VAMP2 to another through a DNA handle (13). The experiment was started with a single preassembled SNARE complex containing truncated syntaxin (187–265) and VAMP2 (25–92) and full-length SNAP-25 (4, 14) to avoid misassembled SNARE by-products (10, 15).

The protein-DNA conjugate extended with the increasing pulling force in a nonlinear manner predicated by the worm-like chain model (Fig. 1B and fig. S2). However, the monotonic force and extension curves were interrupted by abrupt changes caused by SNARE disassembly or reassembly (Fig. 1C). Fast reversible transitions appeared in two force regions, the first in the range of 8 to 13 pN with  $\sim 3$ -nm average extension change (Fig. 1D and fig. S3) and the second in the range of 14 to 19 pN with  $\sim 7$ -nm extension change (Fig. 1D and fig. S4). Both transitions occurred between two states (fig. S5 and table S1), manifesting two distinct binary switches in SNAREs. When the linker domain (LD) of VAMP2 was deleted, the first transition disappeared, whereas the second transition remained (fig. S6). Thus, the first transition is caused by reversible folding and unfolding of the LD alone. The average size of the extension change sug-

gests that a total of  $22 (\pm 3, \text{SD})$  amino acids or 10 amino acids in VAMP2 (83–92) participated in the transition (fig. S7A). This observation is consistent with a fully zippered LD in a coiled-coil conformation in solution (Fig. 1B, state 1) as seen in the crystal structure of the SNARE complex (4, 16). Further deletion into the C-terminal SNARE domain of VAMP2 (Vc) abolished the second transition (fig. S8), which suggests that this VAMP2 region is involved in the transition.

The additional  $\sim 7$ -nm extension increase from the LD unfolded state (Fig. 1B, state 2) leads to a partially zippered SNARE state (state 3, Fig. 1E). To derive the structure, energy, and kinetics associated with this state, we measured the real-time transition involving Vc at different mean forces (Fig. 1D). The fast two-state transition was confirmed by hidden-Markov modeling (HMM) (17) and the histogram distribution of extension (figs. S5B and S9). On the basis of the measured extension change and an asymmetrical transition model (fig. S10) (18), we found that  $26 (\pm 3)$  amino acids in VAMP2 (57–82) were unzipped in the partial SNARE complex (Fig. 1E). This places the interface of the unzipped Vc and the zippered N-terminal VAMP2 (Vn) at residue 56 ( $\pm 5, \text{SD}$ ;  $\pm 1, \text{SEM}$ ) or at the central ionic layer of the bundle. This ionic layer is one of the most evolutionarily conserved features of all SNAREs (19), yet with unclear functions. Thus, our result suggests a possible role of the ionic layer in stabilizing the half-zipper neuronal SNARE structure crucial for regulation of membrane fusion (7, 8, 12, 18, 20).

The half unfolding probability of Vc (Fig. 2A) determines an average equilibrium force ( $f_{eq}$ ) of  $17 (\pm 2 \text{ SD}, n = 76)$  pN, which can be defined as the maximum force output of Vc zippering averaged over the accompanying extension change. This force is the highest equilibrium force reported for any coiled-coil proteins (17), including the designed strongest known coiled coil designated as pIL with an equilibrium force of 12.4 pN (21). The unfolding probability could be extrapolated to zero force (14, 17, 22) to reveal the Vc zippering free energy of  $28 (\pm 3) k_B T$ , higher than the folding energy of pIL [ $24 (\pm 1) k_B T$ ] despite pIL's greater length (33 amino acids) (21).

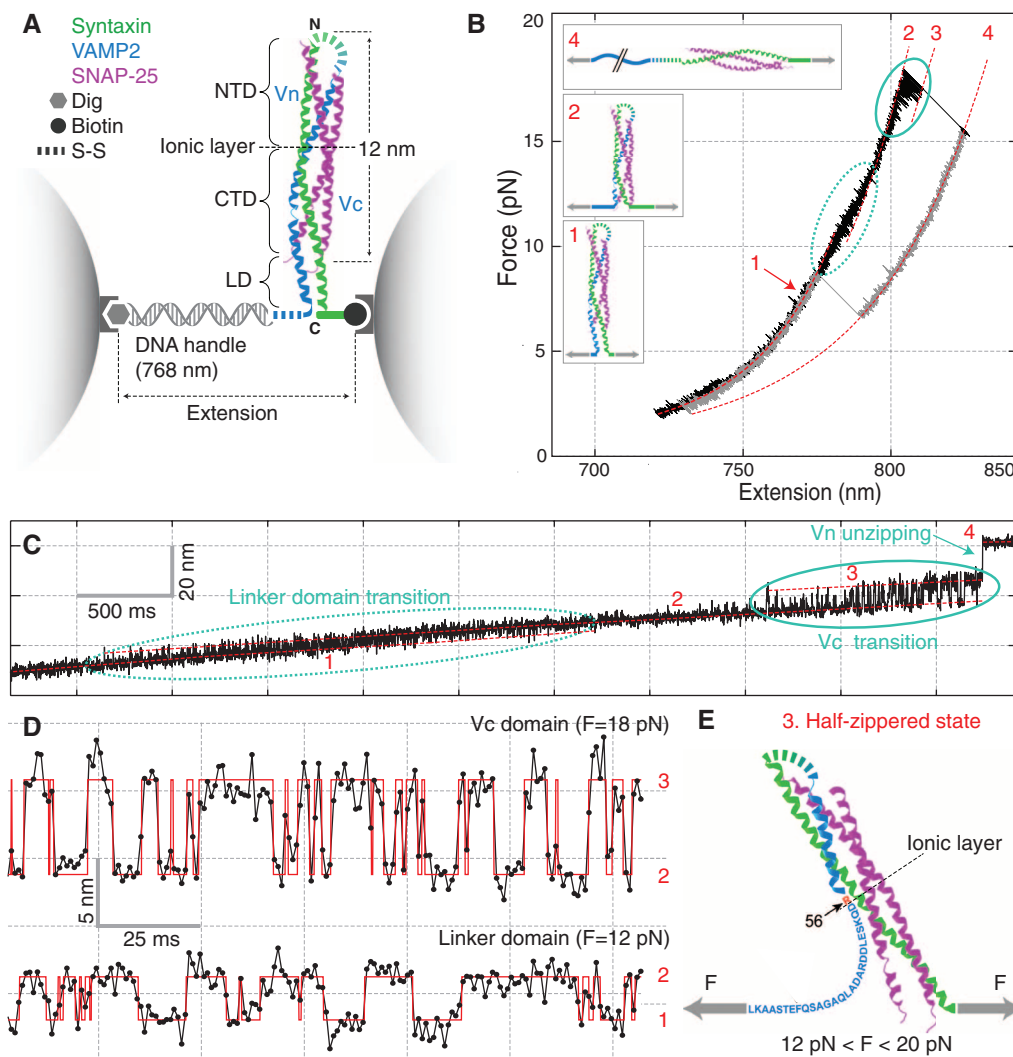
The average Vc zippering rate at the maximum force output ( $\sim 160 \text{ s}^{-1}$ ) (Fig. 2B) is also greater than the equilibrium rate of pIL ( $\sim 10 \text{ s}^{-1}$ ) (21). Yet the rate is much less than the estimated

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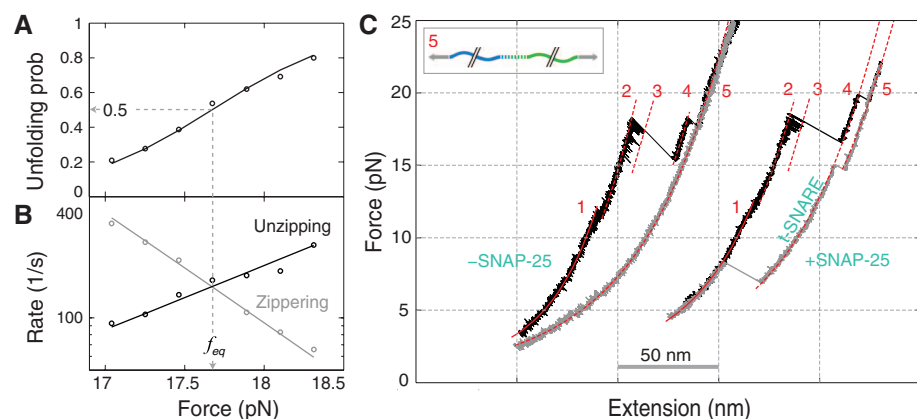
**Fig. 1.** Dynamic disassembly and re-assembly of the single SNARE complex.

(A) Experimental setup. The SNARE complex contains the N-terminal (NTD) and C-terminal (CTD) SNARE domains, with the corresponding VAMP2 regions designed as Vn and Vc, respectively, separated by the ionic layer and the linker domain (LD). (B) Force-extension curve (FEC) of the SNARE-DNA conjugate. The FEC corresponds to the first of five cycles of pull (black) and relaxation (gray) shown in fig. S2. Different segments of the FEC can be fit by the worm-like chain model (red dashed lines), revealing the structures of SNARE assembly states (inset, same red numbering throughout the figures). The LD and CTD transitions are marked by dashed and solid ovals, respectively. (C) Time-dependent extension corresponding to the pulling phase from 8.6 to 17.5 pN (fig. S3). (D) Extension transitions of LD (bottom) and CTD (top) with their idealized transitions determined by the HMM analysis (red traces). The histogram distributions of extension are shown in fig. S5. (E) Structural model of the force-dependent half-zipped state with Vc unzipped to the ionic layer (red).



SNARE zippering rate of  $4 \times 10^4 \text{ s}^{-1}$  commensurate with the time required for synaptic vesicle fusion ( $\sim 60 \mu\text{s}$ ) (23). However, the Vc zippering rate increases exponentially as the opposing force drops (Fig. 2B) (17), reaching the required rate for synaptic fusion at a predicted force of 14 pN. This means that a single SNARE complex in principle can generate a high average force of 14 pN during membrane fusion. When further extrapolated to zero force (14), the Vc zippering becomes downhill and barrierless, with a rate estimated to be  $\sim 1 \times 10^6 \text{ s}^{-1}$  (21), corresponding to the rate of the coil-to-helix transition and diffusion of the Vc polypeptide (24). This fast zippering rate is partially attributed to the largely ordered t-SNARE complex that serves as a template for Vc zippering (figs. S10 and S11) (18). In conclusion, the extraordinarily high force output, energy, and rate qualify Vc zippering as the major power stroke for the fast synaptic fusion (11).

Similarly, we measured a folding energy of  $8 (\pm 2) k_B T$  for LD (fig. S7, B and C) with a maximum force output close to that of pIL ( $\sim 12$  pN). An energy barrier of  $5 (\pm 2) k_B T$  was derived, corresponding to a zipping rate of  $7 \times 10^3 (9 \times 10^2$



**Fig. 2.** SNAP-25-dependent SNARE assembly. (A) Force-dependent unzipping probability of CTD measured on a single SNARE complex. (B) Corresponding CTD transition rates. Theoretical predictions are shown in lines. (C) FECs measured in the absence (–SNAP-25) and presence (+SNAP-25) of SNAP-25 in solution.

to  $5 \times 10^4 \text{ s}^{-1}$  at zero force. LD also strongly and rapidly zippers, which may transduce and augment the Vc zippering energy to drive membrane fusion. LD's zippering rate and energy may be in-

creased by transmembrane domains (25) and proteins such as synaptotagmin and Munc18-1 (3, 26).

The Vc transition generally ended with an irreversible extension jump of  $15 (\pm 1) \text{ nm}$  (Fig. 1,



B and C, from states 3 to 4), corresponding to complete Vn unzipping (fig. S12). When immediately relaxed, the SNARE complex first followed a different force-extension curve (FEC) to reach lower force (Fig. 1B). As the force was lowered to 3 to 10 pN, the complex fully and cooperatively reassembled.

The dynamic disassembly and reassembly of a single SNARE complex could be repeated for many cycles of pull and relaxation (fig. S2). However, when the t-SNARE complex was pulled to a higher force (in the range of 15 to 28 pN), one additional irreversible extension jump was observed (Fig. 2C, from states 4 to 5, and fig. S11). No more transitions were seen when further pulling to even higher forces (>30 pN), indicating complete unfolding of the SNARE complex (state 5). Thus, this jump may correspond to unfolding of the remaining t-SNARE complex. When relaxed to low forces (<3 pN), a majority (~85%) of syntaxin and VAMP2 conjugates could not reassemble (Fig. 2C and fig. S2), suggesting dissociation of the SNAP-25 molecule.

To further test the dependence of SNARE assembly on SNAP-25, we repeated the above experiment by adding SNAP-25 in the solution. Single SNARE complexes were fully disassembled by being pulled to high forces and then relaxed to detect SNARE reassembly. At 0.2  $\mu$ M SNAP-25, the ternary SNARE complex could reassemble at a low force (3 to 10 pN) with a probability of ~0.8 for each round of relaxation (Fig. 2C). This reassembly was always followed by formation of the t-SNARE complex in a higher force range (>12 pN). The SNAP-25 molecule

in solution could bind to the syntaxin-VAMP2 conjugate and initiate de novo SNARE assembly. Comparing this to the experiment in the absence of SNAP-25 suggests that the binary t-SNARE is required for SNARE zippering (27). In contrast, the affinity between syntaxin and VAMP2 in the absence of SNAP-25 is minimal and could not be detected in our experiments (Fig. 2C) (10, 28).

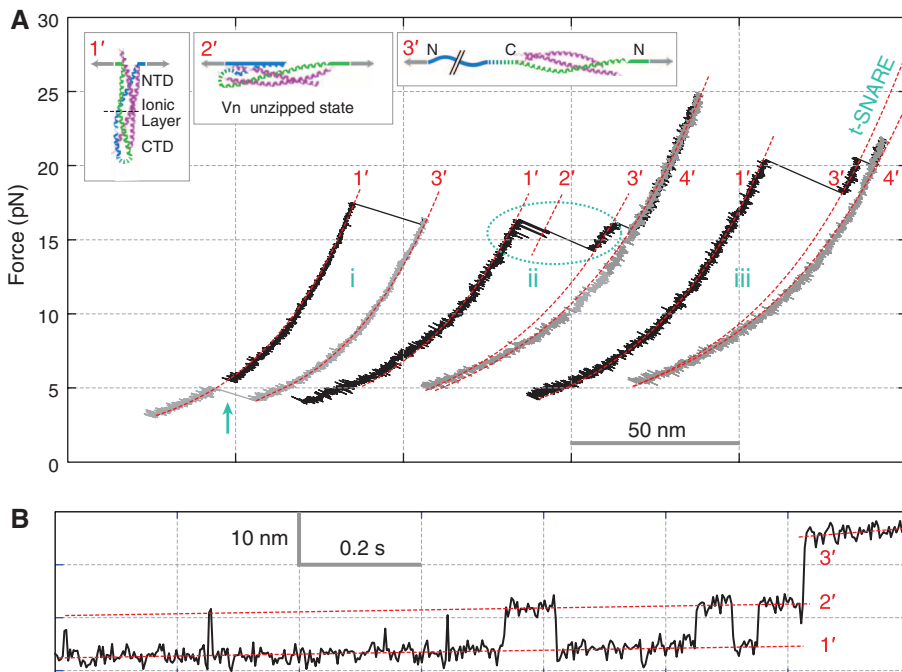
The assembly and disassembly of the N-terminal domain (NTD) occurred with a large force hysteresis, indicating a large energy barrier for NTD transitions and preventing us from measuring its association energy. To gain insight into NTD's assembly mechanism, we pulled a single SNARE complex from the N-termini of syntaxin and VAMP2 (Fig. 3A) (14). The SNARE complex unzipped into t- and v-SNAREs (from states 1' to 3') in two parallel pathways. About two-thirds of the 53 complexes tested showed one-step unzipping (FECs i and iii), whereas other complexes exhibited two-step unzipping via a transient intermediate state (state 2'). Reversible transitions were often observed between this state and the fully zippered state 1' (Fig. 3B) and lasted long enough for the equilibrium transition force and the average extension change to be determined. This partially zippered SNARE complex had Vn unzipped to residue 57 ( $\pm 3$ , SEM), or approximately the ionic layer. The Vn domain unzipped at a higher average equilibrium force of 18.5 ( $\pm 0.4$ , SEM) pN than Vc from C-terminal pull at 16.7 ( $\pm 0.2$ , SEM) pN. In addition, the average extension change of Vn ( $8.3 \pm 0.2$ , SEM, nm) was greater than that of Vc ( $7.1 \pm 0.1$ , SEM, nm). These

measurements allow an estimation of the folding free energy of 35 ( $\pm 4$ )  $k_B T$  for NTD assembly in the presence of the preassembled C-terminal domain (CTD) (14, 17). However, Vn assembled much more slowly than Vc (Fig. 3B).

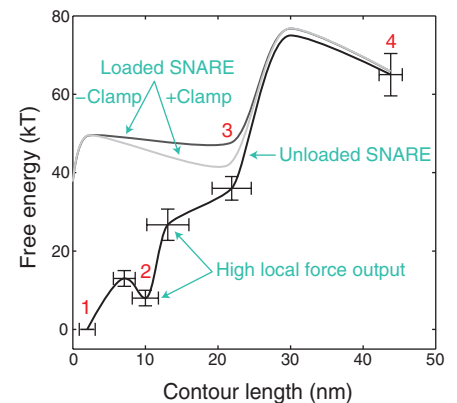
The t-SNARE complex again remained intact after VAMP2 was pulled out (Fig. 3, state 3'). This complex has a structure similar to those obtained from the C-terminal pull (table S1). On average, the t-SNARE complex contained 61 ( $\pm 4$ ) helical amino acids in the syntaxin molecule, suggesting an approximately fully assembled three-helix bundle for the t-SNARE (figs. S10 and S11). Upon relaxation, the ternary complex could reassemble at an average force of 3.2 ( $\pm 0.2$ , SEM) pN (Fig. 3, FEC i), compared to 5.0 ( $\pm 0.2$ , SEM) pN from the C-terminal pull. The more force-sensitive assembly of the SNARE complex from the N-terminal pull indicates that initiation of the assembly occurs in NTD (10, 17, 29).

We suggest a model for three-stage neuronal SNARE assembly through sequential zippering of NTD, CTD, and LD (fig. S13). Overall, SNARE assembly outputs free energy of 65 ( $\pm 6$ )  $k_B T$  (14). This energy is much higher than in previous reports (28, 30, 31), but justified by our equilibrium measurements required for any thermodynamic quantifications (14). These measurements lead to the energy landscape of SNARE zippering (Fig. 4). The CTD zippering energy is enriched at its C-terminal end or in VAMP2 (74–82), leading to a higher local force generation (~34 pN) (fig. S8) (30).

The half-zippered state appeared to exist only in the force range of 12 to 20 pN. Below this force range, the state collapsed into the four-helix bundle, consistent with its downhill folding at zero force. Thus, SNARE domain zippering became a two-state process limited by the slow NTD assembly (10, 28). Above this range, the half-zippered state completely unzipped. The half-zippered state



**Fig. 3.** Disassembly and reassembly of the SNARE complex under N-terminal pulling force. **(A)** FECs and their segmental fit (red dashed line) showing different assembly states (inset) including the completely unfolded state 4'. The full SNARE reassembly (cyan arrow) is t-SNARE dependent. **(B)** Extension-time trace corresponding to the region marked in the dashed oval in **(A)**.



**Fig. 4.** Sketches of the energy landscapes for SNARE zippering in the absence (black) and presence of the opposing force load from membranes with (light gray) and without (gray) complexin clamp. The contour length of the SNARE complex between the C termini of syntaxin (residue 265) and VAMP2 (residue 92) is chosen as a reaction coordinate. Error bars show the SDs of the measurements.

could be further stabilized by synaptotagmin and complexin (12, 18, 20) (Fig. 4).

The elegant molecular logic of the SNARE complex thus revealed perfectly fits to precise regulation of neurotransmitter release (3), with slow intrinsic assembly of NTD to allow control of vesicle priming by regulatory factors that accelerate NTD assembly, thereby creating the readily releasable pool of neurotransmitters (11); an intrinsic pause near the ionic layer stabilized by the repulsion between membranes being forced to fuse to enable clamping by complexin at this stage of zippering (17); and unobstructed, fast zippering of CTD and LD to open the fusion pore once the clamp is removed, enabling neurotransmitters to be rapidly released. The pore then expands as the transmembrane domains of VAMP2 and syntaxin dimerize (32).

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**Acknowledgments:** We thank H. Ji and W. Xu for technical assistance and F. Pincet, T. Melia, and E. Karatekin for valuable discussion. This work is supported by NIH grants GM093341 to Y.Z. and DK027044 to J.E.R. Y.Z. designed the experiments; Y.G., S.Z., G.G., Z.X., L.M., and G.S. performed the experiments; Y.Z. and Y.G. analyzed the data; and Y.Z. and J.E.R. wrote the paper. The data and Matlab codes are in the paper and the supplementary materials.

#### Supplementary Materials

www.sciencemag.org/cgi/content/full/science.1224492/DC1  
Materials and Methods  
Figs. S1 to S13  
Table S1  
References (33–68)

9 May 2012; accepted 7 August 2012  
Published online 16 August 2012;  
10.1126/science.1224492

## Highly Conserved Protective Epitopes on Influenza B Viruses

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Identification of broadly neutralizing antibodies against influenza A viruses has raised hopes for the development of monoclonal antibody-based immunotherapy and “universal” vaccines for influenza. However, a substantial part of the annual flu burden is caused by two cocirculating, antigenically distinct lineages of influenza B viruses. Here, we report human monoclonal antibodies, CR8033, CR8071, and CR9114, that protect mice against lethal challenge from both lineages. Antibodies CR8033 and CR8071 recognize distinct conserved epitopes in the head region of the influenza B hemagglutinin (HA), whereas CR9114 binds a conserved epitope in the HA stem and protects against lethal challenge with influenza A and B viruses. These antibodies may inform on development of monoclonal antibody-based treatments and a universal flu vaccine for all influenza A and B viruses.

Influenza viruses continue to cause substantial morbidity and mortality worldwide (1). Because current vaccines are typically only effective against the specific viral strains used for vaccination and closely related viruses (2) and increasing resistance reduces the effectiveness of the available antiviral drugs (3), an urgent need remains for innovative new treatments, both prophylactic and therapeutic (4). To this end, we and others have previously described human monoclonal antibodies (mAbs) that neutralize a wide spectrum of influenza A viruses by binding to highly conserved epitopes in the stem

region of hemagglutinin (HA), the major viral surface glycoprotein (5–9). To date, influenza B viruses have received less attention, because they are largely restricted to humans and thus lack the large animal reservoirs that are key to the emergence of pandemic influenza A viruses (10).

Although the morbidity and mortality rates attributable to influenza B are lower than those for H3N2 viruses, they are higher than those for H1N1 viruses (11). Influenza B viruses are classified as a single influenza type, but two antigenically and genetically distinct lineages cocirculate (12), represented by the prototype viruses

B/Victoria/2/1987 (Victoria lineage) and B/Yamagata/16/1988 (Yamagata lineage) (13). Vaccine manufacturers have therefore recently initiated clinical evaluation of quadrivalent vaccines that include strains from each influenza B lineage, H1N1, and H3N2 (14). Given that influenza B viruses are the major cause of seasonal influenza epidemics every 2 to 4 years leading to substantial absenteeism, hospitalization, and death (11), mAbs with broad neutralizing activity (bnAbs) against influenza B viruses have important clinical potential.

Combinatorial display libraries, constructed from human B cells of volunteers recently vaccinated with the seasonal influenza vaccine (9), were panned by using soluble recombinant HA from various influenza A and B viruses, and phages were subsequently screened for binding to HAs

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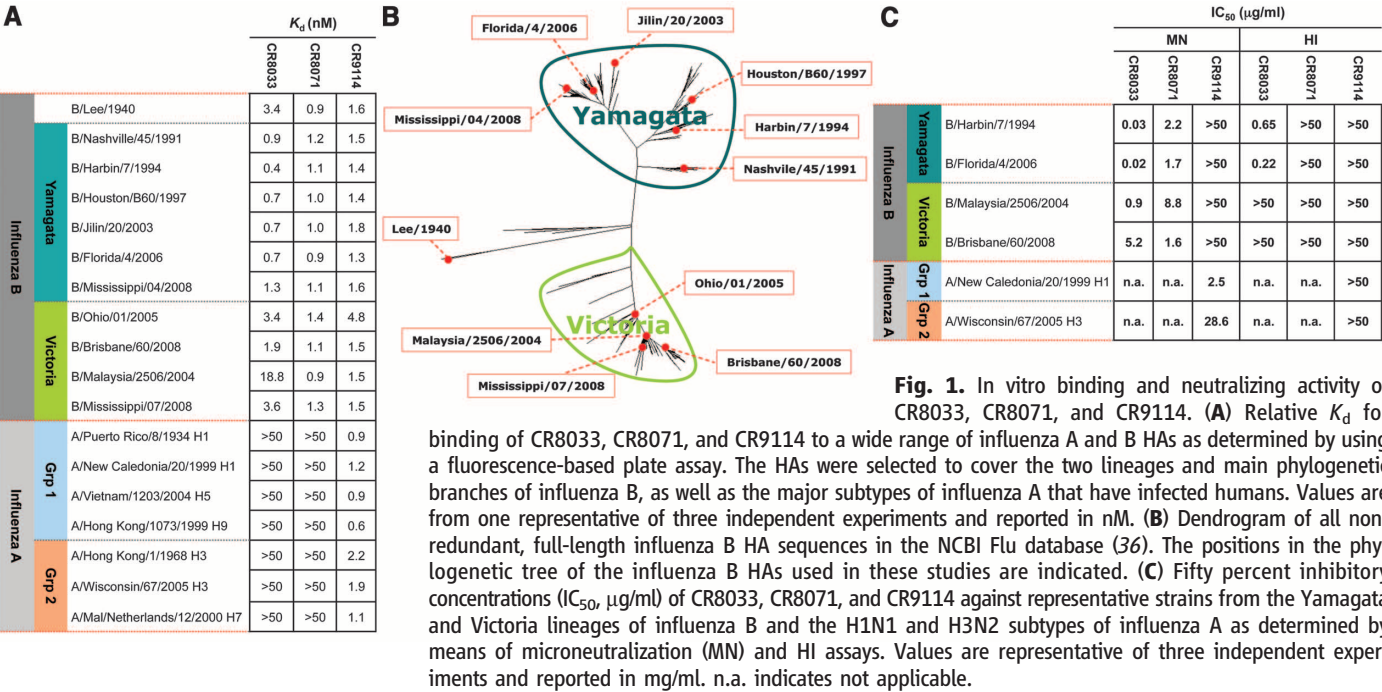
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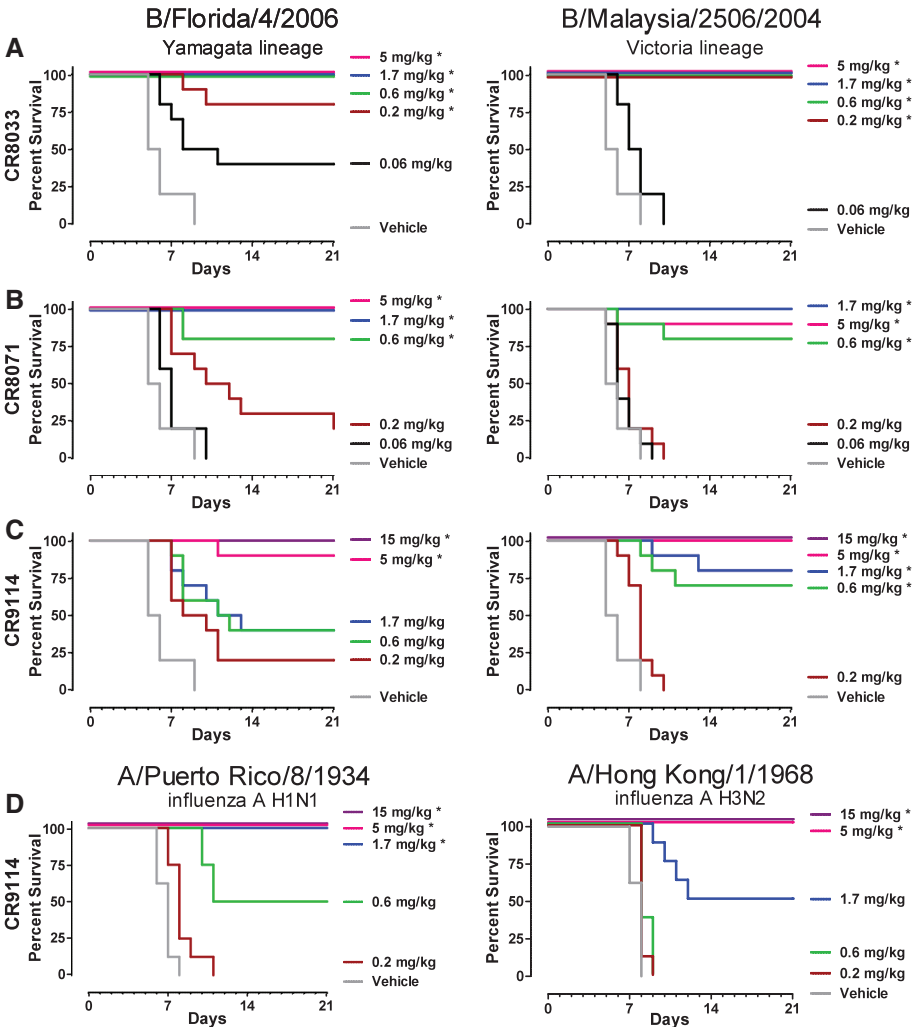
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**Fig. 2.** In vivo efficacy of CR8033, CR8071, and CR9114. Efficacy of CR8033 (A), CR8071 (B), and CR9114 (C) against lethal challenge with mouse-adapted B/Florida/4/2006 (left) or B/Malaysia/2506/2004 (right) virus and (D) of CR9114 against mouse-adapted A/Puerto Rico/8/1934 (left) or A/Hong Kong/1/1968 virus (right). Survival curves of mice [10 animals per group in (A) to (C), 8 per group in (D)] treated with the indicated doses of CR8033, CR8071, or CR9114, or vehicle control 24 hours before challenge by intranasal inoculation (at day 0), are shown. Asterisks indicate significant improvements in survival proportions at day 21 compared with vehicle control ( $P < 0.05$ ).





of both influenza B lineages (15). We recovered three immunoglobulins (IgGs) that bound HAS from both lineages, CR8033 ( $V_H$ 3-9 and  $V_K$ 3-20) and CR8071 ( $V_H$ 1-18 and  $V_K$ 1-47) (Fig. 1, A and B), as well as CR9114, a  $V_H$ 1-69 antibody, which additionally binds influenza A viruses from both group 1 and group 2 (Fig. 1A and fig. S1). Importantly, CR8033 and CR8071 neutralized representative viruses from either lineage (Fig. 1C), whereas polyclonal sheep sera did not (table S1). CR8033 showed hemagglutination-inhibition (HI) activity against the Yamagata lineage but not against the Victoria lineage. Thus, whereas CR8033 likely neutralizes Yamagata strains by blocking receptor binding, it appears to neutralize Victoria strains by another mechanism. In contrast, CR8071 showed no HI activity against either lineage. Although CR9114 neutralized all influenza A viruses tested, it did not show in vitro

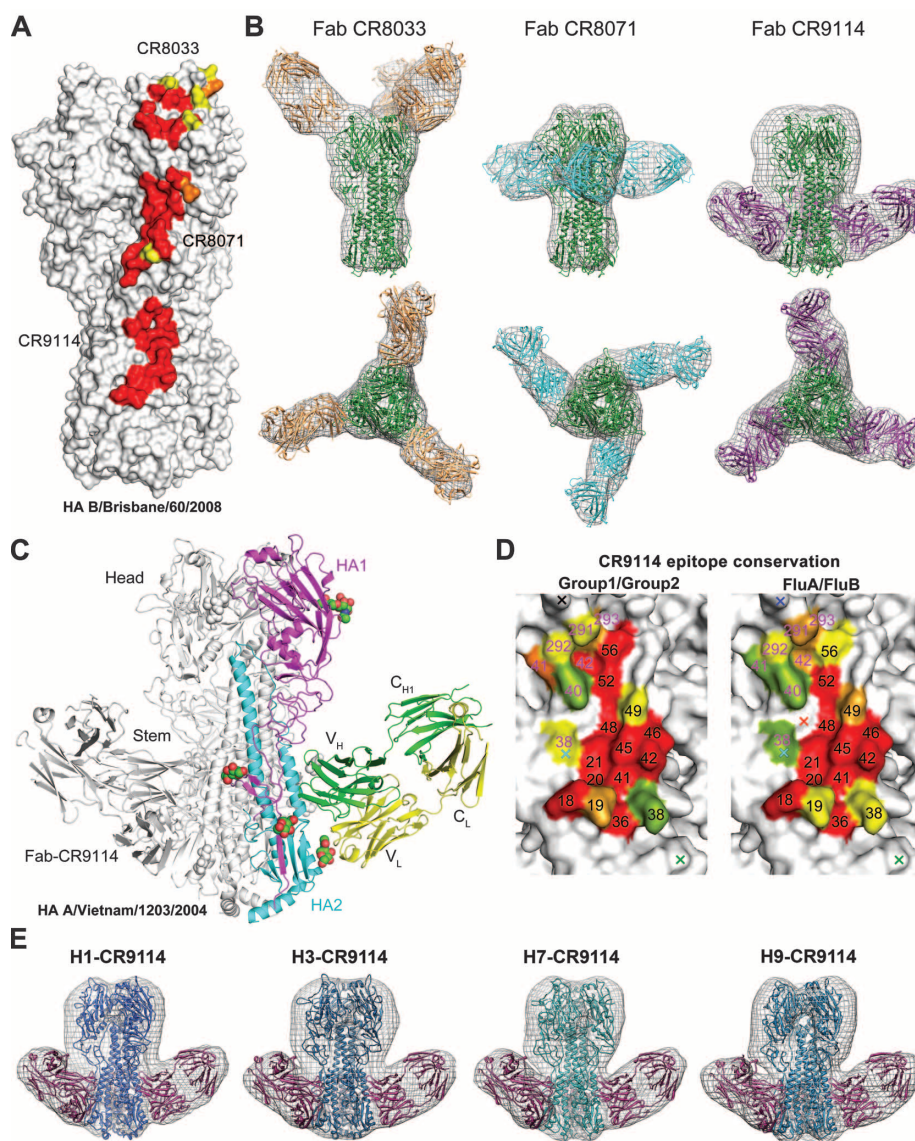
neutralizing activity against influenza B viruses at the tested concentrations (Fig. 1C). Because recent work indicated that the protective efficacy of broadly neutralizing influenza antibody F16 is substantially dependent on antibody effector functions (5), we evaluated the protective efficacy of all three mAbs against B/Florida/4/2006 (Yamagata) and B/Malaysia/2506/2004 (Victoria) infections in mice.

Doses as low as 0.6 mg/kg and 0.2 mg/kg of CR8033 fully protected mice from lethality upon challenge with B/Florida/4/2006 and B/Malaysia/2506/2004, respectively, and lower doses still resulted in increased survival and reduced weight loss (Fig. 2A and fig. S2A). Although CR8071 is somewhat less potent in vivo than CR8033 (Fig. 2B and fig. S2B), the difference is less marked than expected on the basis of the microneutralization assay, indicating that in vitro neutralization

is not fully predictive of in vivo potency. Despite the apparent lack of in vitro neutralizing activity, 15 mg/kg and  $\geq 5$  mg/kg of CR9114 fully protected mice from lethality after challenge with B/Florida/4/2006 and B/Malaysia/2506/2004, respectively, with significant protection against the latter virus with 1.7 and 0.6 mg/kg (Fig. 2C and fig. S2C). Similarly, 1.7 and 5 mg/kg CR9114 protected mice against challenge with lethal doses of influenza A H1N1 and H3N2 viruses, respectively (Fig. 2D and fig. S2D).

CR8033, CR8071, and CR9114 do not compete with each other for HA binding, suggesting that they recognize different epitopes (fig. S3). However, CR9114 competes with CR6261 and CR8020 (fig. S4), suggesting that it binds an HA stem epitope. To identify their epitopes and understand how they achieve broad neutralization, we obtained x-ray and electron microscopy (EM)

**Fig. 3.** CR8033, CR8071, and CR9114 bind to distinct epitopes on influenza B HA and conservation of the CR9114 neutralizing epitope on influenza A and B. **(A)** Surface representation illustrating the neutralizing epitopes on HA B/Brisbane/60/2008 of CR8033, CR8071, and CR9114 as determined from the EM structures in (B) and the crystal structures of CR9114 in (C) and CR8071 in fig. S8. The EM density maps allow unambiguous fits of known structures with good correspondence with the CR9114 epitope defined by both x-ray crystallography and EM, despite differences in resolution. The structure is colored by conservation of contact residues across all available influenza B virus sequences: red, over 98% conserved; orange, 75 to 98% conserved; yellow, 50 to 75% conserved. **(B)** Negative stain EM reconstructions (gray mesh) of CR8033 (left), CR8071 (middle), and CR9114 (right) in complex with B/Florida/4/2006. Side (top row) and overhead (bottom row) views show the fits of the individual crystal structures of the Fabs and flu B HA to the EM density. **(C)** Crystal structure of CR9114 in complex with H5 HA (group 1). One HA/Fab protomer of the trimeric complex is colored with HA1 in magenta, HA2 in cyan, Fab heavy chain in green, Fab light chain in yellow, and N-linked glycans in colored balls representing their atom type. The other two protomers are colored in gray. **(D)** Conservation of CR9114 contact residues across all 16 influenza A subtypes (left) and between influenza A and B viruses (right). Red, orange, and yellow correspond to coloring used in (A), with green indicating 25 to 50% conserved. Carbohydrates positions are represented by a cross colored in black (group 1), cyan (group 2), green (group 1 and 2), orange (influenza B), and blue (influenza A and B). Residue numbers are shown with HA1 in magenta and HA2 in black. **(E)** Illustration of cross-reactivity of CR9114 for influenza A (from left to right) H1, H3, H7, and H9 subtypes using negative stain EM. Single-particle reconstructions of negatively stained CR9114 Fabs bound to HA trimers from four major subtypes of influenza A that have infected humans (SC1918/H1, group 1; HK68/H3, group 2; Neth03/H7, group 2; and Wisc66/H9, group 1). The HA trimers are colored in different shades of blue. The Fabs of CR9114 (three per trimer) are colored in purple (the third Fab, at the back, has been omitted for clarity). Broadly neutralizing CR9114 binds in a structurally similar manner to the stem region across all subtypes, groups, and classes of HA. Additional density in the HA not accounted for by the protein likely corresponds to glycosylation.





structures for CR8033, CR8071, and CR9114 (Fig. 3) in complex with representative HAs of influenza A and B viruses.

We generated a 3D reconstruction of the HA ectodomain of B/Florida/4/2006 in complex with Fab CR8033 (Fig. 3B) by using negative stain electron microscopy (EM). Crystal structures of Fab CR8033 at 1.9 Å and influenza B/Brisbane/60/2008 HA ectodomain at 3.45 Å provided atomic models for fitting into the EM reconstruction (fig. S5 and tables S2 to S5). Three CR8033 Fabs bind the HA trimer on an epitope overlapping the receptor-binding pocket and surrounding antigenic sites. The EM model suggests that almost all contacts are made by variable region of heavy chain ( $V_H$ ) using all three heavy-chain complementarity-determining region (HCDRs) loops and framework 3 (fig. S6) (16). Although the receptor-binding pocket of influenza B HA is well conserved, variability in surrounding residues (fig. S7) may account for differences in CR8033 binding and neutralization of the two influenza B lineages.

EM reconstructions were also performed on Fab CR8071 in complex with both B/Florida/4/2006 (Yamagata) and B/Malaysia/2506/2004 HAs (Victoria) (Fig. 3B and fig. S8D), along with

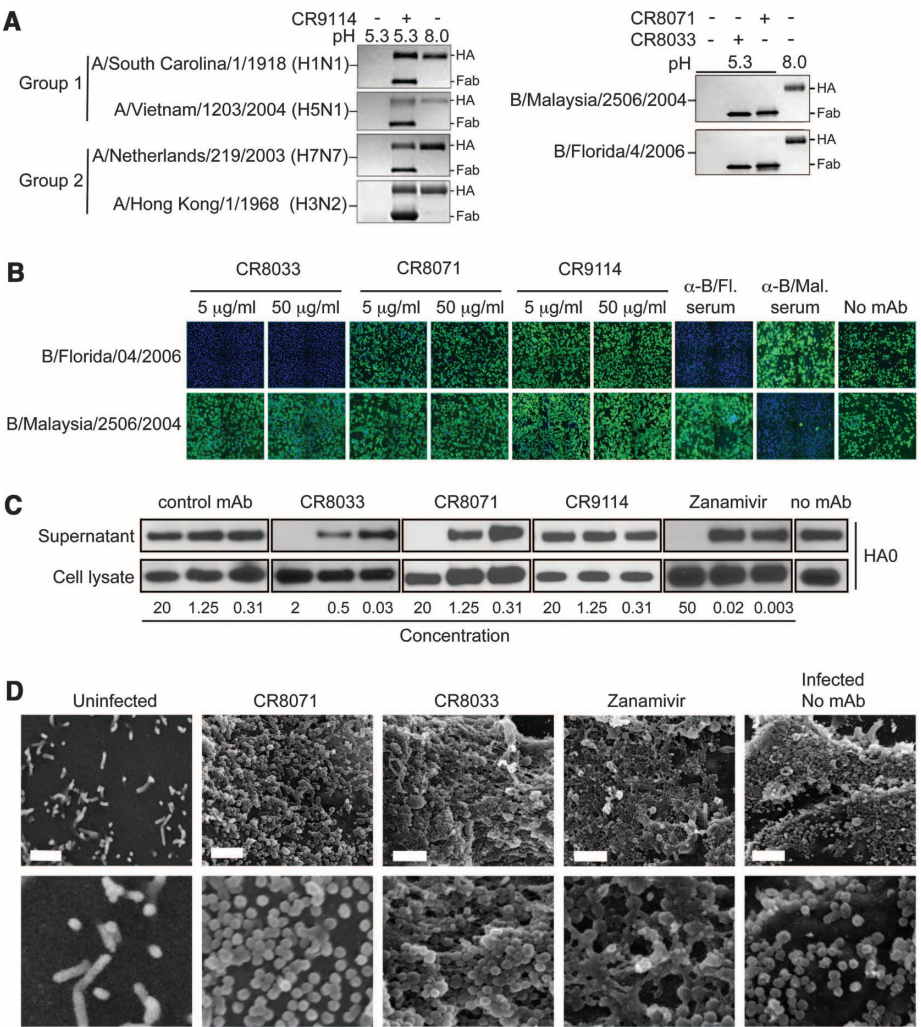
crystal structures of Fab CR8071 with a B/Florida/4/2006 HA1 construct (2.7 Å) and CR8059, of which CR8071 is a stabilized variant (see supplementary materials), with B/Brisbane/60/2008 HA (5.65 Å) (fig. S8, A to C). CR8071 binds the vestigial esterase domain at the base of the HA head distant from the receptor-binding site and in an orientation (Fig. 3B) consistent with the observed lack of HI. The epitope is highly conserved in influenza B HA, with 17 of 19 residues >98% conserved.

Crystal structures were determined for Fab CR9114 with HAs from a highly pathogenic H5N1 virus (A/Vietnam/1203/2004; Viet04/H5, 1.7 Å) (Fig. 3C), as well as H3 (5.25 Å) and H7 (5.75 Å) (fig. S9). EM studies further illustrated the CR9114 cross-reactivity with influenza A H1, H3, H7, and H9 subtypes and influenza B (Fig. 3E). CR9114 binds the HA stem (fig. S10), recognizing an epitope nearly identical to that of CR6261 (17) by using the same HCDR loops (1, 2, 3) and FR3 with no light-chain contacts. Recently, human antibody FI6 was identified that broadly neutralizes influenza A viruses by targeting about the same epitope (5). However, FI6 uses a different V gene ( $V_H$ 3-30) and its light chain (fig. S11) and

is rotated by  $\sim 90^\circ$  compared with  $V_H$ 1-69 antibodies CR6261 and CR9114. Thus, FI6 represents an alternative solution to cross-group neutralization of influenza A but not influenza B viruses.

The CR9114 epitope is highly conserved in essentially all influenza A subtypes and influenza B (Fig. 3D and tables S6 and S7). At least three obstacles must be overcome for an antibody to bind to a similar epitope across influenza A and B. First, most group 1 HAs have HA2 Thr<sup>49</sup>, whereas most group 2 HAs have a larger Asn (fig. S10 and table S6) (6, 18) that can be accommodated by CR9114. Second, polymorphisms at HA2 position 111, His (group 1), Thr/Ala (group 2), or Glu (influenza B), result in subtly different conformations of HA2 Trp<sup>21</sup>, which affect its ability to make favorable interactions with hot spot residue HCDR2 Phe<sup>54</sup> in CR6261 (fig. S10) (19). The more favorable orientation and approach of Phe<sup>54</sup> and the apparent plasticity of the CR9114 combining site (20) (fig. S12) may allow CR9114 to make high-affinity interactions (including a hydrogen bond) with the various conformations of Trp<sup>21</sup> in group 1 and group 2 HAs. Third, the predominant conformation of a conserved glycan at HA1 Asn<sup>38</sup> in H3, H7, H10, and H15 in group 2,

**Fig. 4.** Neutralization mechanisms of CR8033, CR8071, and CR9114. **(A)** CR9114 protects HAs of group 1 [A/South Carolina/1/1918 (H1N1) and A/Vietnam/1203/2004 (H5N1)] and group 2 [A/Netherlands/219/2003 (H7N7) and A/Hong Kong/1/1968 (H3N2)] influenza A viruses from the pH-induced protease sensitivity associated with membrane fusion. Exposure to low pH converts the HAs to the postfusion state, rendering them sensitive to trypsin digestion (lane 1 versus 3), but CR9114 prevents this conversion, retaining the HA in the protease-resistant, pre-fusion form (lane 2). CR8033 and CR8070 do not prevent this conversion at low pH (right) ( $V = 4$ ). **(B)** Expression of influenza NP in monolayers of MDCK cells 16 to 18 hours after inoculation with B/Florida/4/2006 or B/Malaysia/2506/2004 viruses that were pre-incubated with CR8033, CR8071, CR9114, or polyclonal sheep sera directed against B/Florida/4/2006 or B/Malaysia/2506/2004, as indicated. NP expression is determined by immunofluorescence. Representative images of three independent experiments are shown. **(C)** Immunoblots of uncleaved HA (HA0) detected in the lysate and supernatant of MDCK cells infected with B/Florida/4/2006 virus and subsequently (from 3 to 20 hours postinfection) incubated with different concentrations of antibodies or zanamivir as indicated. HA0 was detected by using rabbit serum against B/Jiangsu/10/03 (Yamagata lineage). Concentrations are in  $\mu\text{g/ml}$  and  $\mu\text{M}$  for antibodies and zanamivir, respectively. Results from one representative of two independent experiments are shown. **(D)** SEM images of the surface of MDCK cells infected with B/Florida/4/2006 virus and subsequently (from 3 to 20 hours postinfection) incubated with CR8071 (10  $\mu\text{g/ml}$ ), CR8033 (2.5  $\mu\text{g/ml}$ ), or zanamivir (60  $\mu\text{M}$ ). Representative images of three independent experiments are shown. Scale bar, 1  $\mu\text{m}$ .



and at HA1 Asn<sup>332</sup> in influenza B, would obscure the epitope surface (figs. S10 and S11) (21–23). Thus, this glycan and Asn side chain must be able to adopt a permissive alternative conformation as observed in the CR9114-H3 crystal structure (24). Displacement of the HA1 38 glycan appears essential for CR9114 binding to several influenza A subtypes, and a similarly positioned glycan at HA1 332 in influenza B must also be avoided (fig. S11). Such glycan flexibility at HA1 38 was also observed in the F16 structure with H3 HA, but, in this case, the glycan at 332 in flu B may be more difficult to avoid (25).

CR9114 and CR6261 both use the V<sub>H</sub>1-69 germline V gene and have relatively small numbers of somatic mutations compared with other bnAbs (26, 27). However, only five mutations are shared (fig. S13), and, hence, they are not simple variants of one another. Aside from the heavy-chain-only binding, both antibodies are fairly conventional, in contrast to many bnAbs to other viruses, such as HIV-1, that have unusual features, such as extensive hypermutation, long indels in one or more CDRs, tyrosine sulfation, or domain swapping (26, 27). Consequently, antibodies like CR9114 are likely to be readily generated and may be present in the repertoire of many individuals, suggesting that an appropriate vaccination strategy may be able to selectively amplify such cross-reactive clones and trigger a bnAb response (4, 28, 29).

Despite CR8033 and CR8071 binding to the more variable HA globular head but consistent with the apparent high level of epitope conservation, escape variants could only be generated after extensive passaging. For B/Florida/4/2006 virus, no CR8033 escape variants were generated in 20 passages, whereas 15 passages were required to generate Lys<sup>38</sup>→Glu<sup>38</sup> (Lys38Glu) and Tyr40His mutants with reduced CR8071 susceptibility. For B/Malaysia/2506/2004 virus, 15 passages were required to generate a Pro161Gln reduced susceptibility mutant for CR8033, whereas 20 rounds of passaging did not result in any CR8071 escape variants. Lys<sup>38</sup> and Pro<sup>161</sup> are highly conserved (99.4% and 100%, respectively) in all 494 (unique) full-length influenza B HA sequences in the National Center for Biotechnology Information (NCBI) database. Although Tyr<sup>40</sup> is only 29.1% conserved, all other strains have His<sup>40</sup>, including B/Harbin/7/94, B/Malaysia/2506/04, and B/Brisbane/60/08, which are effectively neutralized by CR8071 (Fig. 1C). In contrast, the Lys38Glu mutation has not been observed in any influenza B isolates. Because CR9114 does not neutralize influenza B viruses in vitro, no influenza B escape variants could be generated (30).

The identification of conserved neutralizing epitopes in the influenza B HA globular head parallels the recent identification of such epitopes in influenza A viruses (31, 32) and establishes that both the HA stem and head regions contain broadly protective epitopes. Whereas the stem-binding CR9114 blocks the HA pH-induced conformational changes associated with membrane

fusion (Fig. 4, A and B, and figs. S14 and S15) (33), this mechanism is not applicable to CR8033 and CR8071 that bind the head region (Fig. 4A). Indeed, whereas CR8033 has HI activity and blocks viral infection when preincubated with B/Florida/4/2006 virus, it had no such effect on B/Malaysia/2506/2004 virus (Fig. 1C and Fig. 4B). Furthermore, CR8071 did not prevent infection of cells by either virus (Fig. 4B) (34).

These antibodies appear to prevent propagation of viruses without preventing entry and genome replication (Figs. 1C and 4B). Thus, we assessed the effect of CR8033 and CR8071 on formation of viral progeny from infected cells. Whereas HA was readily detected in both lysates and supernatants of Madin-Darby canine kidney (MDCK) cell cultures that were first infected and subsequently incubated with a nonbinding control antibody or CR9114, no HA could be detected in the supernatants upon incubation with CR8033 or CR8071, despite abundant HA in the lysate (Fig. 4C). The effects of CR8033 and CR8071 then resemble that of neuraminidase inhibitor zanamivir, which interferes with release of progeny virions from infected cells (35). Indeed, the dense aggregation of virions on the surface of infected cells, particularly in the presence of antibody CR8033, closely resembles that observed in zanamivir-treated cells as examined by scanning electron microscopy (SEM) (Fig. 4D).

The identification and characterization of monoclonal antibodies with broad neutralizing activity against influenza B viruses, together with previously described broadly neutralizing antibodies against group 1 and group 2 influenza A viruses (6, 7, 9), bring a universal therapy a step closer and may serve as guides for design of broadly protective vaccines. In particular, a vaccine that elicits antibodies targeting the CR9114 epitope may provide the ultimate goal of protection against all influenza A and influenza B viruses.

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- Materials and methods are available as supplementary materials on Science Online.
- We have previously shown (our previous control analyses of CR6261 and other known HA-Fab complexes) that, because we have high-resolution crystal structures of HAs and antibodies, the fit to the density is excellent and generally unambiguous. Nevertheless, the lower resolution of these data does not permit as precise a definition of the Ab epitope.
- This epitope consists of residues from the N- and C-terminal regions of HA1 (38, 40 to 42, and 291 to 293), and the N-terminal portion of HA2 (18 to 21, 36, 38, 41, 42, 45, 46, 48, 49, 52, 53, and 56), including helix A. CR9114 buries a total of ~1293 Å<sup>2</sup> at the interface with HA (654 Å<sup>2</sup> for HA and 639 Å<sup>2</sup> for Fab).
- Thr<sup>49</sup> is buried by CR6261, and affinity of CR6261 for the SC1918/H1 HA is reduced over 100-fold by a Thr49Asn mutation designed to mimic the group 2 sequence. Further, CR6261 binding to H12 HA (group 1) is undetectable under our assay conditions [binding affinity (*K<sub>d</sub>*) > ~10 μM], likely because of a Thr49Gln substitution. In contrast, CR9114 binds the SC1918/H1 Thr49Asn mutant and H12 HA (Thr49Gln) with high affinity because the conformation of its HCDR1 loop allows the larger Asn and Gln side chains to be accommodated.
- A His111Leu mutation that mimics the group 2 Trp<sup>21</sup> conformation on a group 1 background drastically reduces CR6261 binding and correlates with virus escape from neutralization (9).
- HCDRs 1, 2, and 3 adopt substantially different conformations in the unbound CR9114 and the CR9114-H5 complex crystal structures, suggesting that these loops may be quite flexible in solution (fig. S12) and allow the antibody to adapt to the subtle variation seen in the largely conserved epitope in HA proteins from different virus subtypes and types.
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- This alternate glycan configuration is supported by the observation of additional electron density near Asn<sup>38</sup> in the CR8020-H3 crystal structure, indicating at least two accessible glycan conformations (7). Although not modeled explicitly, the second conformation would move the glycan away from the epitope and facilitate antibody binding.
- Although isolate-specific variation in residues proximal to the epitope may also influence interaction of F16 with influenza B, one possible problem is the Tyr100C at the tip of HCDR3 that makes an H bond with Thr<sup>318</sup> (group1/2) in the hydrophobic groove at the junction between helix A and HA1 (fig. S10). In influenza B, the equivalent residue is a glycosylated Asn<sup>332</sup>, which will likely lead to a steric clash with Tyr100C of F16. CR9114 does not interact with Thr<sup>318</sup>, and the orientation of the HCDR2 loop allows CR9114 to accommodate larger residue at this position (figs. S10 and S11).
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- No escape variants were generated; however, two substitutions previously described to affect neutralization of group 2 and group 1 influenza A viruses by CR8020 and CR6261, respectively, also affected CR9114 binding. Asp19Asn affects H3 and H7 viruses and reduces H3 binding (~30-fold increase in *K<sub>d</sub>*). In addition, all influenza B viruses have Ala<sup>19</sup>, which may account in part for the somewhat lower affinity for influenza B. In contrast, several group 1 subtypes with Asp19Asn or Asp19Ala mutations are neutralized by CR9114 and/or bound with high affinity, presumably because other substitutions offset the detrimental effect of substitutions at position 19. The Asp19Asn variant is rare in most subtypes, suggesting that most viruses will be sensitive



- to CR9114 (table S7) (7). The other Ile45Phe escape variant is naturally present in essentially all human H2N2 viruses that circulated from 1957 to 1968, and Phe45Ile substitution in a human H2 HA restores high affinity binding for both CR6261 and CR9114 (table S8). In contrast, Phe<sup>45</sup> occurs in only 3 of 8550 sequences from avian H2N2 isolates and the remaining 15 subtypes.
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  33. Why influenza B viruses are not neutralized in the same way by CR9114 remains currently unknown.
  34. In contrast, polyclonal sheep sera directed against B/Florida/4/2006 and B/Malaysia/2506/2004 did prevent initial infection, but not of virus from the opposite lineage.
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**Acknowledgments:** We thank J. Juraszek; B. Brandenburg; M. Koldijk; K. Hegmans; J. Meijer; N. Hafkemeier; A. Apetri; J. Dulos; L. Dekking; H. Vietsch; G. Perdok; H. Tien; D. Marciano; the staff of the Advanced Photon Source (APS) GM/CA-CAT 23ID-B and 23ID-D, Stanford Synchrotron Radiation Lightsource (SSRL) BL11-1 and SSRL BL7-1, and Advanced Light Source (ALS); X. Dai; R. Stanfield; W. Yu; J. P. Julien; R. N. Kirchdoerfer; and E. Brown of Ottawa University, Canada, for the mouse-adapted A/Hong Kong/1/68 strain. Crystallization experiments were carried out on the Rigaku Crystallization system at the Joint Center for Structural Genomics, which is supported by the National Institute of General Medical

Sciences (NIGMS) Protein Structure Initiative U54 GM094586. The EM and image analysis was conducted by R.K., J.H.L., and Z.M. at the National Resource for Automated Molecular Microscopy, which is supported by NIH through the National Center for Research Resources' P41 program (RR017573). This project has been funded in part by the Area of Excellence Scheme of the University Grants Committee, Hong Kong (grant AoE/M-12/06); a predoctoral fellowship from the Achievement Rewards for College Scientists Foundation (D.C.E.); grant GM080209 from the NIH Molecular Evolution Training Program (D.C.E.); a Saper Aude Postdoc grant from the Danish Council for Independent Research, Natural Sciences (N.S.L.), and the Skaggs Institute (I.A.W.). Portions of this research were carried out at the SSRL, a national user facility operated by Stanford University on behalf of the U.S. Department of Energy (DOE), Office of Basic Energy Sciences. The SSRL Structural Molecular Biology Program is supported by the DOE Office of Biological and Environmental Research and by NIH, National Center for Research Resources, Biomedical Technology Program (P41RR001209), and the NIGMS. The GM/CA CAT 23-ID-B beamline has been funded in whole or in part with federal funds from National Cancer Institute (Y1-CO-1020) and NIGMS (Y1-GM-1104). Use of the APS was supported by the DOE, Basic Energy Sciences, Office of Science, under contract no. DE-AC02-06CH11357. The content is solely the responsibility of the authors and does not necessarily represent the official views of NIGMS or the NIH. The ALS is supported by the director, Office of Science, Office of Basic Energy Sciences, of the DOE under contract no. DE-AC02-05CH11231. Coordinates and structure factors are deposited in the Protein Data Bank (PDB code 4FQH for CR9114 Fab, 4FQI for CR9114 Fab-A/H5 HA, 4FQJ for CR8071

Fab-B/Florida HA1, 4FQK for CR8059 Fab-B/Brisbane HA, 4FQL for CR8033 Fab, 4FQM for B/Brisbane HA, 4FQY for CR9114 Fab-A/H3 HA, and 4FQV for CR9114 Fab-A/H7 HA). Image reconstructions have been deposited at the EMDataBank under accession numbers EMD-2143 (CR8033/Florida), EMD-2144 (CR8071/Florida), EMD-2145 (CR8071/Malaysia), EMD-2146 (CR9114/Florida), EMD-2147 (CR9114/H1), EMD-2148 (CR9114/H3), EMD-2149 (CR9114/H9), and EMD-2150 (CR9114/H7). Nucleotide sequences for the CR8033, CR8059 (CR8071), and CR9114 variable regions have been deposited in GenBank [accession numbers JX213635 (CR8033, V<sub>H</sub>), JX213636 (CR8033, V<sub>L</sub>), JX213637 (CR8059, V<sub>H</sub>), JX213638 (CR8059, V<sub>L</sub>), JX213639 (CR9114, V<sub>H</sub>), and JX213640 (CR9114, V<sub>L</sub>)]. Patent applications relating to antibodies CR8033, CR8059, CR8071, and CR9114 have been filed (CR8033, CR8059, and CR8071 are claimed in EP 12158525.1 and U.S. 61/608,414. CR9114 is claimed in EP 11173953.8 and U.S. 61/572,417). Sharing will be subject to standard material transfer agreements. This is publication 21741 from the Scripps Research Institute.

## Supplementary Materials

www.sciencemag.org/cgi/content/full/science.1222908/DC1  
Materials and Methods  
Figs. S1 to S18  
Tables S1 to S8  
References (37–62)

4 April 2012; accepted 9 July 2012  
Published online 9 August 2012;  
10.1126/science.1222908

# Structural Probing of a Protein Phosphatase 2A Network by Chemical Cross-Linking and Mass Spectrometry

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The identification of proximate amino acids by chemical cross-linking and mass spectrometry (XL-MS) facilitates the structural analysis of homogeneous protein complexes. We gained distance restraints on a modular interaction network of protein complexes affinity-purified from human cells by applying an adapted XL-MS protocol. Systematic analysis of human protein phosphatase 2A (PP2A) complexes identified 176 interprotein and 570 intraprotein cross-links that link specific trimeric PP2A complexes to a multitude of adaptor proteins that control their cellular functions. Spatial restraints guided molecular modeling of the binding interface between immunoglobulin binding protein 1 (IGBP1) and PP2A and revealed the topology of TCP1 ring complex (TRiC) chaperonin interacting with the PP2A regulatory subunit 2ABG. This study establishes XL-MS as an integral part of hybrid structural biology approaches for the analysis of endogenous protein complexes.

Cellular processes can rarely be attributed to the activity of a single protein. Instead, proteins act in functional modules, such as macromolecular complexes or signal transduction

networks. Gaining mechanistic insights into the function of multisubunit modules is facilitated by structural elucidation (1, 2). Chemical cross-linking, in combination with mass spectrometry (XL-MS), is a low-resolution structural technique for the characterization of the architecture of protein complexes (3, 4). XL-MS provides distance information by identifying spatially proximate lysine residues that have been covalently linked by a bifunctional cross-linking reagent. This approach has been successfully applied to homogenous protein complexes purified for crystallographic purposes (5–8). In contrast to high-resolution structural biology techniques, XL-MS has the potential to acquire spatial restraints from heterogeneous protein samples. We thus ap-

plied this method to characterize the topology of a signaling network by systematic analysis of endogenous protein complexes (Fig. 1).

The abundant protein phosphatase 2A (PP2A) is involved in diverse signaling pathways regulating cell growth, apoptosis, differentiation, cell motility, DNA damage response, and cell cycle progression (9–12). In eukaryotes, active PP2A holoenzymes are heterotrimers composed of a catalytic subunit (C, human isoforms PP2AA and PP2AB), a scaffold subunit (A, human isoforms 2AAA and 2AAB), and one of a large array of regulatory subunits (B, B', B'', and B''', each subfamily consisting of two to five isoforms) (Fig. 2A and table S1) that selectively target PP2A subpopulations to specific substrates (13). To reveal the topology of PP2A holoenzymes in complex with the adaptor proteins that regulate their phosphatase activity and subcellular location, we purified these complexes from human cells and analyzed their topology by combining XL-MS and computational molecular modeling.

We first determined the proteins copurifying with trimeric PP2A holoenzymes by isolating 14 proteins, previously detected in PP2A complexes (14, 15), through an N-terminal His<sub>6</sub>-HA-StrepII-tag from human embryonic kidney cells (fig. S1 and table S2). The associated protein complexes were identified by mass spectrometry (Fig. 1) (16), resulting in a dense interaction network of 94 proteins (Fig. 2A and tables S1 and S3).

To elucidate the topology of the PP2A network, we probed the complexes by XL-MS. Cross-linking was achieved by immobilizing the PP2A complexes on beads (16). Incubation with the appropriate concentration of disuccinimidyl suberate (DSS) (fig. S2) and subsequent proteolysis resulted in a complex mixture of tryptic peptides that was

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analyzed by tandem mass spectrometry (17). Cross-linked peptides were identified by the search engine xQuest (3, 16, 18) (Fig. 1 and fig. S3).

XL-MS analyses of the PP2A complexes associated with the 14 bait proteins were performed at least in duplicate (table S2) and yielded 176 interprotein (Fig. 2B) and 570 intraprotein cross-links. As various interactions were repeatedly detected within the PP2A network, we further assessed the confidence of cross-link identifications by counting the number of fragment ion spectra in the data set and the number of experiments detecting a specific cross-link (tables S4 and S5).

Cross-link assignments were further evaluated by measuring the distances between the two lysine residues on x-ray structures and comparative models of the human protein complexes identified in the PP2A network (fig. S4 and tables S4 to S6) (16). The median Euclidean C $\alpha$ -C $\alpha$  distances for the charted 70 interprotein and 287 intraprotein peptide pairs were 19.6 Å and 15.4 Å, respectively (Fig. 2C). Of these cross-links, 92% were below 30 Å, the estimated maximum threshold for the Euclidean distance spanned by DSS, accounting for protein dynamics and model inaccuracies (fig. S5) (16). Thus, cross-link-derived spatial restraints can guide computational modeling and protein-protein docking studies.

The closest human relatives of the PP2A catalytic subunits within the phosphoprotein phosphatase family are PP4C and PPP6 (11). Reciprocal pull-downs of 2A5D, PP2AA, and PP4C indicate that subunits of PP2A and PP4 copurify (Fig. 2A and table S3) (19). Cross-links suggest that P4R3A, the regulatory subunit of PP4, occupies a position similar to the regulatory B' subunit 2A5G on the PP2A scaffold subunit 2AAA, thus assembling a P4R3A/2AAA/PP4C hybrid complex (Fig. 2B and tables S3 and S4) (20).

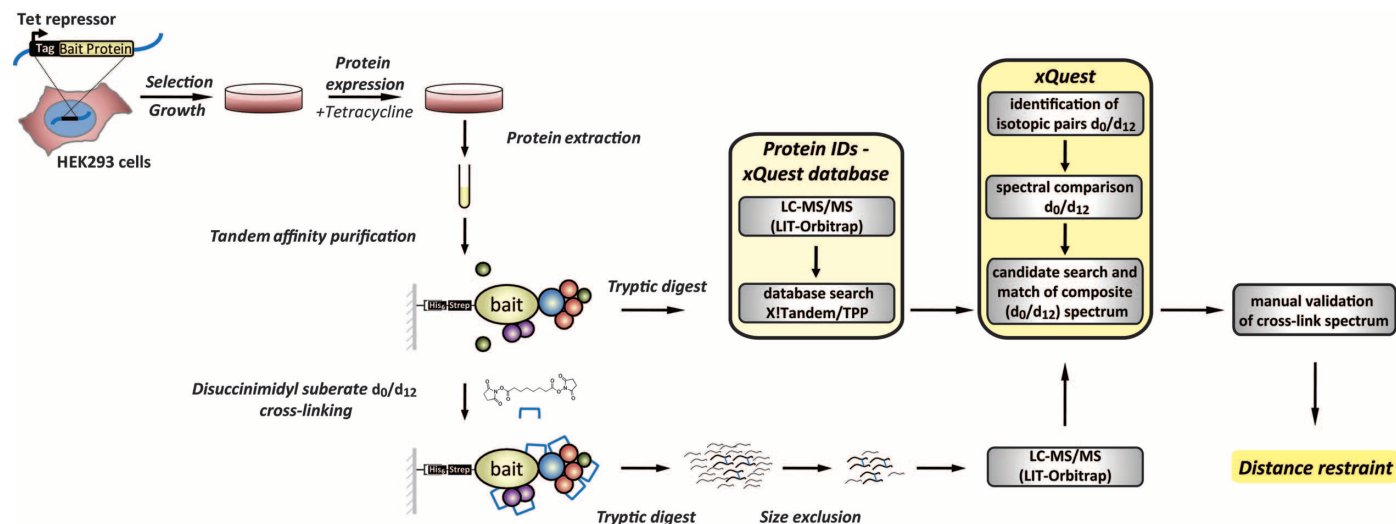
The catalytic subunits PP2AA, PP2AB, PP4C, and PPP6 were previously shown to form heterodimeric complexes with immunoglobulin binding protein 1 (IGBP1), which inactivates the catalytic

subunits and prevents their proteasomal degradation until functional phosphatase complexes are assembled (21). Previous binding studies revealed that residue E42 of PP2AA (22) and residues R155 and K158 of IGBP1 (23, 24) are essential for the interaction of IGBP1 with the catalytic subunits. To locate the binding interface between IGBP1 and the catalytic subunits PP2AA and PP4C, we used seven and three interprotein restraints, respectively, to guide molecular modeling. Starting from the crystal structure of the N-terminal 221 amino acids of mouse IGBP1 (23), we first localized the C-terminal domain within a full-length human structural model of IGBP1 by de novo modeling using the Rosetta software suite (25) and intraprotein cross-links, including 18 within the C terminus and 32 between the C- and N-terminal domains (fig. S6 and table S7) (16). Protein structures of PP2AA and IGBP1 were subjected to the docking protocol of Rosetta (26), resulting in 1075 docking models that clustered into 237 groups (Fig. 3A). The 300 docking models with the shortest average distance for the seven identified IGBP1-PP2AA cross-links clustered into four large groups (Fig. 3B) (16). This strategy yielded a defined 1447 Å<sup>2</sup> binding interface displaying residues E37 of PP2AA and K163 of IGBP1 at the interface in 95% of the docking models (Fig. 3C; fig. S7, A and B; figs. S8 to S10; and table S8). The interface to PP4C was less constrained because it was defined by only three distance restraints (fig. S7, C to F, and tables S9 and S10) (16). We detected the previously identified interface residues E42 of PP2AA (22) at a frequency of 32% and R155 and K158 of IGBP1 (23, 24) in 43% and 5% of the modeled interfaces, respectively (Fig. 3C and table S11). Mutating K163 in IGBP1 to alanine reduced binding to the PP2A catalytic subunits compared with wild-type IGBP1 (Fig. 3D). The R155A IGBP1 mutant completely abrogated interaction, whereas the K158A mutant still bound residual amounts of the catalytic subunits that were further reduced by K158A/K163A double mutation. These re-

sults indicate that K163 of IGBP1, the interface residue most frequently mapped in computational docking experiments, is involved in forming the binding interface with the catalytic PP2A subunits. Consistent with previous studies, we found that binding of IGBP1 and of the PP2A scaffold subunits to the catalytic subunits is mutually exclusive (Fig. 2A and table S3) and that their binding sites on PP2AA minimally overlap (fig. S11) (22). IGBP1 binding may thus prevent interaction of PP2A catalytic and scaffold subunits by steric hindrance and allosteric distortion of the catalytic-scaffold interface rather than by direct competition with the scaffold subunit (21).

Interprotein cross-links unveiled the topology of PP2A complexes mediated by distinct regulatory subunits, such as the B''/striatin-interacting phosphatase and kinase (STRIPAK) complex (Fig. 3E) (14). P2R3C (B'') linked PP2A activity to the centrosomal complex CE350/FR1OP (27) and B and B' subunits were found to be cross-linked to the Integrator complex (14) (Fig. 2B). Covalent linkages indicated that B' proteins recruit PP2A to several adaptor proteins such as LIP1, PRR14, FA13A, and CCDC6 and to a distinct set of cell cycle regulators, including M89BB, ESPL1, and SGOL1 (Fig. 2B and table S4).

SGOL1 specifically targets A/B/C complexes to centromeres, which are thought to dephosphorylate cohesin and thereby prevent precocious cohesin dissociation in mitosis and meiosis (28, 29). Previous x-ray structure determination of a PP2A-SGOL1 complex revealed that residues 51 to 96 of SGOL1 form a parallel homodimeric coiled coil, which is a prerequisite for its binding to PP2A holoenzymes. The N- and C-terminal ends of SGOL1 helices form discrete interfaces with PP2AA and 2A5G, respectively (30). On SGOL1-bound PP2A complexes, we identified 11 SGOL1 intraprotein cross-links and two and three interprotein cross-links to PP2A C or B' subunits, respectively (Fig. 2B and tables S4 and S5). SGOL1 also copurified with the PP2A inhibitor SET and



**Fig. 1.** Schematic outline of the XL-MS workflow established for the identification of chemically cross-linked lysines on affinity-purified human PP2A complexes (16). LC-MS/MS, liquid chromatography coupled to tandem mass spectrometry; LIT, linear ion trap; TPP, trans-proteomic pipeline.

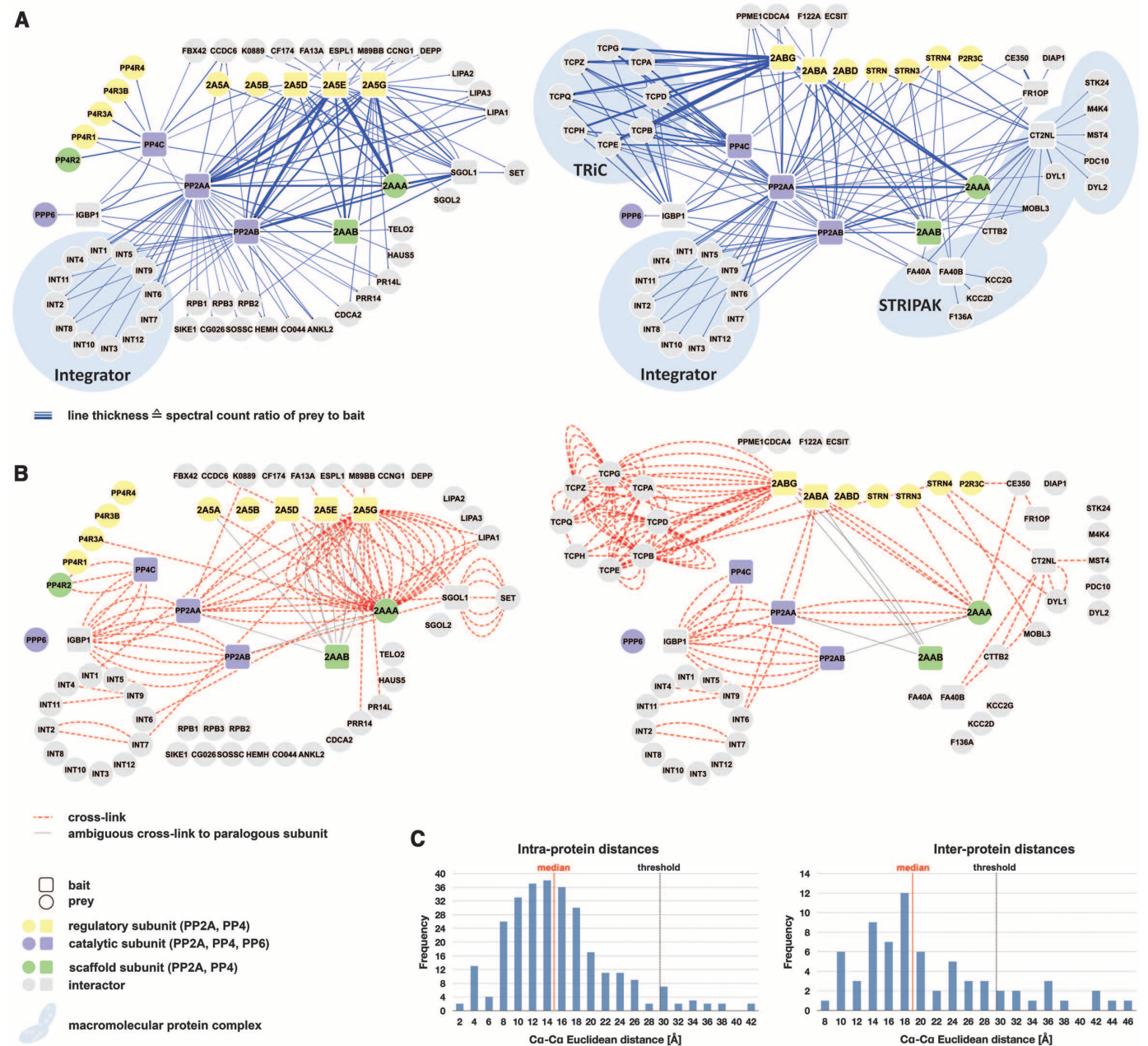


the SGOL1-SET complex was characterized by seven interprotein cross-links (Fig. 3F). Interestingly, the x-ray structure of the SET-TAF1 $\beta$  complex revealed an extended N-terminal helix (33 to 90) undergoing coiled-coil interactions in SET (31), which is of similar length as the SGOL1 helix. It is thus conceivable that a similar coiled-coil interface might be established in the SGOL1-SET complex. The distribution of cross-links between SGOL1 and SET residues suggests an antiparallel arrangement (Fig. 3F) that reveals an array of hydrophobic residues similar to the hydrophobic interactions mediating SGOL1 homo-

dimer formation (Fig. 3, G and H) (30). Together with the observation that SET and SGOL1 copurify with the B' subunit 2A5E (Fig. 2A and table S3) (28), our cross-links suggest that SGOL1 may be involved in recruiting the PP2A inhibitor SET to the catalytic center of PP2A holoenzymes or in maintaining SET binding.

The WD40 propeller-containing regulatory subunits, B and B'', which are presumably in a partially folded state, were found to be cross-linked to subunits of TCP1 ring complex (TRiC), a cylindrical molecular chaperone complex consisting of two hetero-octameric rings (Fig. 2B and

table S4) (32). We identified 54 TRiC intersubunit cross-links consistent with the recently reported subunit topology (Fig. 4A and fig. S4C) (33, 34) and demonstrating that we purified the fully assembled chaperone complex. Isolating TRiC in a stoichiometric complex with endogenous 2ABG (fig. S12) facilitated the identification of 19 cross-links between 2ABG and the N- and C-terminal tails of TRiC subunits, which are located in the equatorial domains (Fig. 4, B and C). Minimizing the distance restraints placed 2ABG at the equatorial plane in the inner cavity of the octameric TRiC ring (Fig. 4C and fig. S13)



**Fig. 2.** Identification of interprotein distance restraints on PP2A protein complexes by XL-MS. **(A)** PP2A protein interaction network based on reciprocal pull-down assays. **(B)** PP2A network topology represented by interprotein cross-links. **(A)** and **(B)** Network is split according to PP2A regulatory subunits. B' (2A5A, 2A5B, 2A5D, 2A5E, and 2A5G) subunits are shown in the left

panel and B (2ABA, 2ABD, and 2ABG), B'' (P2R3C) and B''' (STRN, STRN3, and STRN4) in the right panel. **(C)** Histogram of the Euclidean Ca-Ca distances between cross-linked lysines determined on x-ray structures and comparative models of the PP2A network. Threshold, estimated maximum Ca-Ca distance spanned by the cross-linking reagent.

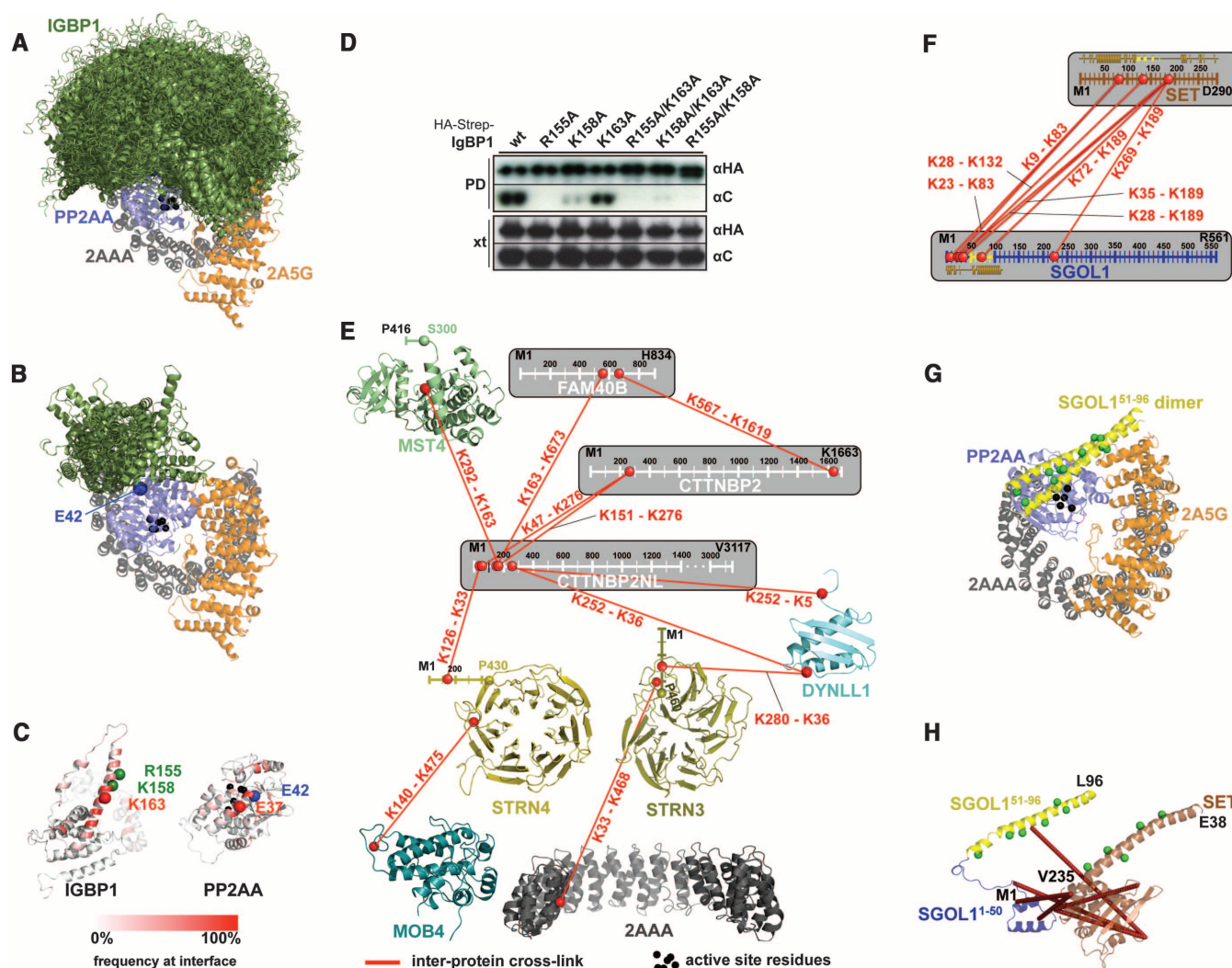


in close proximity to the conserved sensor loops adjacent to the subunit tails (Fig. 4D and table S12) (16). In a recent x-ray study on the tubulin-TRiC complex, these loops have been implicated in substrate interactions, and such contacts may trigger the adenosine triphosphate-driven conformational cycle (35). We performed cryo-electron microscopy (cryo-EM) analysis of the human 2ABG-TRiC complex isolated in an undefined nucleotide state by applying eight fold symmetry averaging. Three-dimensional (3D) reconstruction revealed a complex 145 Å in height and 160 Å in diameter at 23 Å resolution (Fig. 4D and fig. S14) (16). One ring was in an intermediate conformation between the closed and open states, whereas the other exhibited a fully open conformation, similar to the previously observed conformation of group II chaperonins in the presence

of adenosine diphosphate or in nucleotide-free states (32). A globular density was found inside the central cavity at the equatorial domains, consistent with the localization for 2ABG inferred from cross-link distance restraints. Similarly, tubulin is bound to the equatorial domains in the tubulin-TRiC crystal structure (35). Additional density was also observed at the apical domains of the fully open ring, which might be attributed to a residual density of the disordered apical domains or to a protein not resolved by XL-MS. Our results provide further evidence for interactions of TRiC with substrate protein at the bottom of the cavity. In contrast, the bacterial group I chaperonin GroEL appears to exclusively recognize substrates with its apical domains (36, 37).

The identification of cross-linked peptides by our mass spectrometry workflow yielded inter-

residue distances that delineated the topology of a PP2A network in human cells. Molecular modeling and docking supported the integration of complementary structural data that facilitated the localization of the binding interface between IGBP1 and the catalytic subunits of PP2A and PP4 and suggested a mode for targeting the PP2A inhibitor SET to the catalytic center by the PP2A cell cycle adaptor protein SGOL1. Interprotein cross-links were sufficient to describe the subunit topology of the 1-MDa complex TRiC and uncovered the localization of the substrate 2ABG at the equatorial domains of TRiC subunits. This study demonstrates the applicability of XL-MS to acquire structural data from heterogeneous protein preparations in a systematic manner and highlights the potential of hybrid structural biology approaches (38) that integrate cross-link-derived

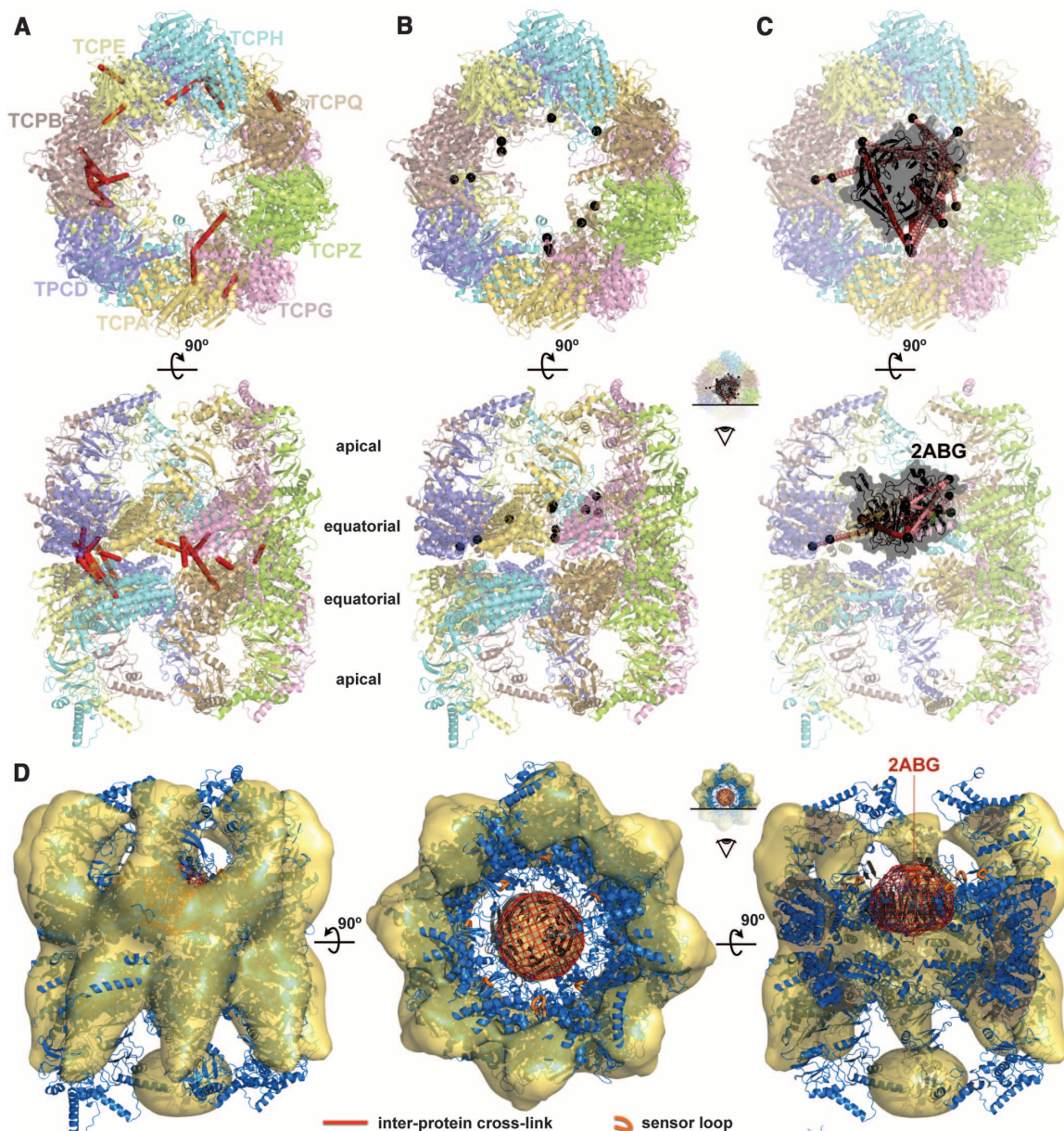


**Fig. 3.** Topology of PP2A-associated protein complexes by applying cross-links to guide computational modeling and docking. (A to C) Identification of the IGBP1-PP2AA binding interface using distance restraints in protein-protein docking experiments (13). (A) Docking models of IGBP1 and PP2AA by superimposing 237 IGBP1 cluster representatives (green) on a PP2AA/2AAA/2A5G complex (PDB entry 3FGA). (B) Four cluster representatives of IGBP1-PP2AA docking models with the shortest average distance for interprotein cross-links. (C) Frequency of amino acid residues mapped to the interface in IGBP1-PP2AA

docking models. (D) Pull-down (PD) binding assay. IGBP1 wild-type and mutant proteins were affinity-purified from human cell extracts (xt), and binding of PP2A catalytic (C) subunits was analyzed by immunoblotting. (E) Schematic subunit map of the STRIPAK complex based on interprotein cross-links. (F) Interprotein cross-links detected on a complex of SGOL1 and SET suggest an antiparallel arrangement. (G) Hydrophobic residues (green spheres) essential for SGOL1 homodimerization (PDB entry 3FGA). (H) Scheme of SGOL1 in complex with SET based on cross-links. Green spheres, hydrophobic residues.



**Fig. 4.** Architecture of the TRiC chaperonin bound to its substrate 2ABG. **(A)** The subunit register of the two stacked TRiC rings was indicated by 19 inter-ring cross-links. **(B)** Eleven lysine residues (black spheres) within six TRiC subunits were cross-linked to 2ABG. **(C)** Schematic model of TRiC in complex with its substrate 2ABG based on cross-links. **(D)** Cryo-EM 3D-reconstruction of the 2ABG-TRiC complex. The comparative model of human TRiC (blue) was fitted into the EM 3D structure of TRiC (yellow). A globular density (red mesh representation) was located at the 2ABG position inferred from cross-links.



distance restraints and high-resolution structural information with computational molecular modeling.

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**Acknowledgments:** We thank S. Hauri, A. Frei, and M. Gstaiger for support. Primary mass spectrometry data are available as mzXML files at [www.peptideatlas.org/PASS/PASS00053](http://www.peptideatlas.org/PASS/PASS00053). This work was supported by the EU FP7 project PROSPECTS. F.H. was supported by the European Molecular Biology Organization and by the European Commission (FP7-PEOPLE-IEF). R.A. was supported by the European Research Council advanced grant Proteomics v.3.0.

#### Supplementary Materials

[www.sciencemag.org/cgi/content/full/337/6100/1348/DC1](http://www.sciencemag.org/cgi/content/full/337/6100/1348/DC1)  
Materials and Methods  
Figs. S1 to S14  
Tables S1 to S14  
Boxes S1 to S9  
References (39–86)

5 March 2012; accepted 18 July 2012  
10.1126/science.1221483

# Global Gene Deletion Analysis Exploring Yeast Filamentous Growth

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The dimorphic switch from a single-cell budding yeast to a filamentous form enables *Saccharomyces cerevisiae* to forage for nutrients and the opportunistic pathogen *Candida albicans* to invade human tissues and evade the immune system. We constructed a genome-wide set of targeted deletion alleles and introduced them into a filamentous *S. cerevisiae* strain,  $\Sigma 1278b$ . We identified genes involved in morphologically distinct forms of filamentation: haploid invasive growth, biofilm formation, and diploid pseudohyphal growth. Unique genes appear to underlie each program, but we also found core genes with general roles in filamentous growth, including *MFG1* (*YDL233w*), whose product binds two morphogenetic transcription factors, Flo8 and Mss11, and functions as a critical transcriptional regulator of filamentous growth in both *S. cerevisiae* and *C. albicans*.

*Saccharomyces cerevisiae* can undergo a reversible developmental transition from a single-cell budding yeast form into a multicellular filamentous form (1). This dimorphic switch enables haploid cells to invade agar in response to carbon deprivation (haploid invasive growth) (2, 3) and to form biofilms on semisolid medium (4), whereas diploid cells form chains of elongated cells called pseudohyphae in response to nitrogen starvation (5). In the opportunistic pathogen *Candida albicans*, the capacity to transition between yeast and filamentous growth is correlated to virulence (6). Because some of the key *S. cerevisiae* signaling pathways that con-

trol filamentous growth are highly conserved in *C. albicans* and other more distantly related fungi (6), *S. cerevisiae* provides a model system for the identification of genes controlling fungal dimorphism and pathogenesis.

*S. cerevisiae* filamentous growth is regulated by the nutrient-sensing cyclic adenosine monophosphate (cAMP)–protein kinase A (PKA) pathway (5, 7, 8) and a mitogen-activated protein kinase (MAPK) pathway (9, 10), whose signals converge on *FLO11* (*MUC1*), a downstream effector of both pathways (11). *FLO11* encodes a cell-surface protein that mediates haploid invasive growth, biofilm formation, and diploid pseudohyphal growth phenotypes (12, 13). The *FLO11* promoter is controlled by numerous transcriptional regulators—including Rim101, which is regulated by a complex signaling pathway that also responds to pH stress (14); the PKA-regulated transcription factor Flo8 (11); the MAPK-regulated transcription factor complex Ste12/Tec1 (11, 15); as well as the transcription factor Mss11 that is regulated by both the PKA and the MAPK signal transduction cascades (16). Our understanding of the diverse signals affecting the *FLO11* promoter remains incomplete. Further, the emerging complexities of this regulatory circuitry and others governing filamentous growth necessitate functional genomic analysis of the dimorphic switch.

We amplified a genome-wide set of deletion alleles from the S288c reference strain deletion mutant collection (17) with each deletion construct carrying ~200 base pairs (bp) of flanking DNA for efficient integration and gene replacement. This enabled us to construct a set of gene deletions in the *S. cerevisiae* strain  $\Sigma 1278b$ , which, unlike S288c, is competent for filamentous growth (5). We generated heterozygous diploid deletion mutants and viable haploid mutants of both mating types, which were then mated together to produce homozygous diploid deletion mutants.

In total, we covered ~90% of the strains in the S288c reference collection (table S1) (18). Because the  $\Sigma 1278b$  and S288c genomes are closely related, most deletion mutants should show a similar phenotype; however, some genes may exhibit a background-specific or conditional phenotype (19). We compared a subset of the  $\Sigma 1278b$  and S288c haploid deletion mutants and found that 267 of 298 mutants tested (~90%) exhibited consistent phenotypes in the two strain backgrounds (table S2) (18).

We screened the  $\Sigma 1278b$  deletion mutant collection (Fig. 1 and table S3) and identified 577, 700, and 688 genes, including many of the well-characterized filamentous growth genes, with potential roles in haploid invasive growth, pseudohyphal growth, and biofilm development, respectively (table S3). Although haploid invasive growth and biofilm formation were significantly correlated with fitness ( $r^2 = 0.19$  and  $r^2 = 0.26$ , respectively;  $P < 10^{-100}$ ,  $t$  test relative to random distribution; fig. S1), the majority of mutants identified in these assays (67% haploid invasive growth mutants and 64% biofilm mutants) are not slow growing, suggesting that these genes have roles in filamentous growth that do not affect fitness.

We also screened two *C. albicans* deletion mutant collections for filamentous growth defects (20, 21). One collection is based on genes encoding transcription factors (20), another spans genes involved in a range of different cellular processes (21), and they combine to cover ~13% of the genome. The mutants were scored for enhanced filamentation under conditions that favor yeast-form growth and for reduced filamentation under filament-inducing conditions (fig. S2). In total, 151 of 829 (~18%) of *C. albicans* mutants had altered filamentation in at least one condition (table S4), a hit rate similar to our *S. cerevisiae* screen. We tested whether *C. albicans* orthologs of the *S. cerevisiae* morphogenetic regulators identified in our  $\Sigma 1278b$  screen were enriched for altered filamentation phenotypes and found 104 of the  $\Sigma 1278b$  *S. cerevisiae* genes that influence morphogenesis with *C. albicans* orthologs; 43 of 104 (~41%) of these mutants had altered filamentation (table S4), with significant enrichment for morphogenetic regulators ( $P < 0.0001$ ,  $\chi^2$  test).

We identified genes required specifically for each one of the developmental programs, including polyamine biosynthetic genes (Fig. 2), required for biosynthesis of spermine, which were required only for pseudohyphal growth and whose defect was rescued by exogenous spermine (fig. S3). We focused on a set of 61 genes required for all three filamentous growth programs (defined as “core” genes) (Fig. 2 and table S3). Notably, the deletion mutants for the majority of core genes with previously unknown roles in filamentous growth were reconstructed and retested for similar phenotypes. Haploid invasive growth and biofilm formation phenotypes were confirmed for 43/46 (93%) and 45/46 (98%) of haploid mutants tested, respectively (table S5). Moreover,

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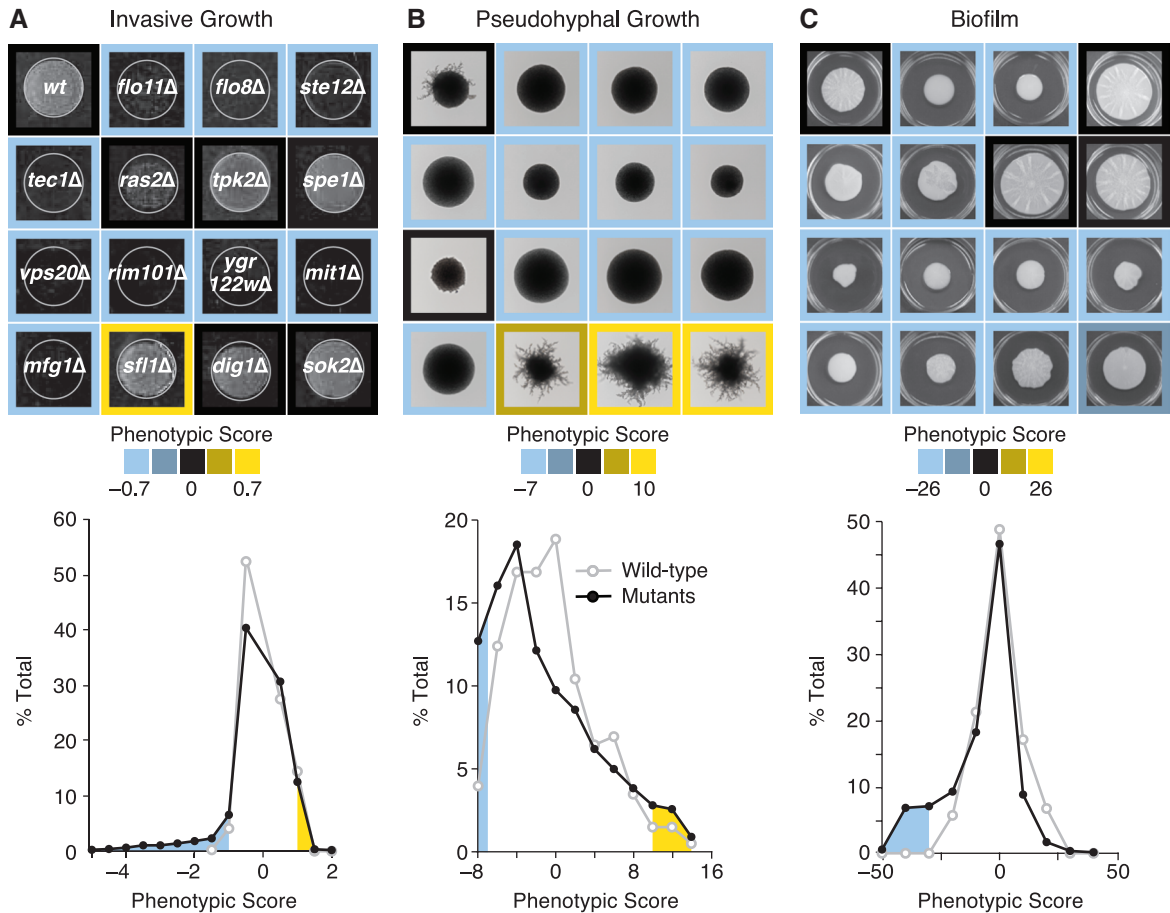
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the pseudohyphal growth phenotype was also confirmed for all 16 homozygous diploid mutants tested (table S5). *FLO11* is critical for all forms of filamentous growth, and a number of the core genes code for proteins that regulate *FLO11* expression, including three components of the Rpd3L histone deacetylase complex, 10 members of the Rim101 signaling pathway, and four *FLO11* transcriptional regulators: Mit1, Tec1, Flo8, and Mss11. The core filamentous growth set also contained a previously uncharacterized gene, *MFG1* (*YDL233W*) (Fig. 2). The relative expression of a *FLO11pr-GFP* reporter, in which the *FLO11* promoter drives the expression of green fluorescent protein (GFP), enabled us to test genes for roles in *FLO11* expression. Indeed, in a colony assay, deletion mutants of known positive regulators of *FLO11* expression exhibited reduced *FLO11pr-GFP* expression, whereas *dig1Δ* cells, which lack a negative regulator, showed increased *FLO11pr-GFP* expression (Fig. 3A and fig. S4). Similar results were observed in a biofilm assay (fig. S4). The *mfg1Δ* deletion mutant also showed

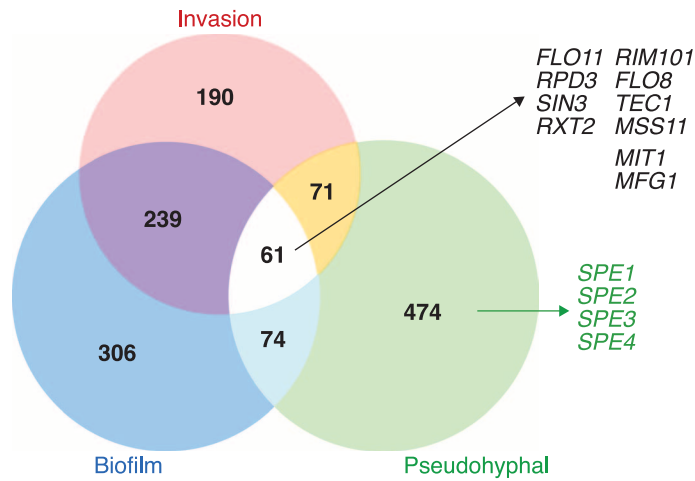
reduced *FLO11pr-GFP* expression (Fig. 3A) and exhibited extreme phenotypes in our quantitative filamentous growth assays, similar to the phenotype associated with the deletion mutants of *FLO8* and *MSS11*, which encode important transcriptional regulators of filamentous growth (Fig. 1 and table S3). Consistent with a filamentous growth transcriptional regulatory role, we found that an Mfg1-GFP fusion protein localized to the nucleus in  $\Sigma 1278b$  cells (fig. S5). Although Mfg1 does not contain a characterized DNA-binding motif, Mfg1 physically interacts with Flo8 and Mss11, which bind directly to the *FLO11* promoter (Fig. 3B). Furthermore, chromatin immunoprecipitation (chIP) analysis demonstrated that Mfg1 associates with the *FLO11* promoter in a region that overlaps with the Flo8-binding domain (–1.1 kb from the AUG codon), and it does so in a Flo8- and Mss11-dependent manner (Fig. 3C). chIP analysis also showed that the binding of Flo8 and Mss11 to the *FLO11* promoter was reduced in the absence of Mfg1, suggesting that Mfg1 may control *FLO11*

gene expression as part of a promoter-bound complex with Flo8 and Mss11. In order to assess the global spectrum of genes regulated by Mfg1, Flo8, and Mss11, we performed calling-card analysis, which identifies promoters bound by transcription factors in vivo (18, 22). At a *P* value cutoff of  $10^{-4}$ , 154 promoters were bound significantly by Mfg1, 174 bound by Flo8, and 268 bound by Mss11 (table S6). In total, 136 of the Mfg1-bound promoters overlapped those bound by Flo8 ( $P < 6.4 \times 10^{-226}$ , hypergeometric test), and 118 of the Mfg1-bound promoters overlapped those bound by Mss11 ( $P < 2.2 \times 10^{-128}$ , hypergeometric test), with 111 Mfg1-bound promoters overlapping with both Flo8 and Mss11 (Fig. 3D). Mfg1, Flo8, and Mss11 all directed calling cards to the *FLO11* promoter as well as promoters of genes involved in *FLO11* expression, and 45 of the Mfg1-, Flo8-, and Mss11-bound promoters regulate genes that lead to filamentous growth phenotypes when deleted. We performed calling-card analysis in a Flo8-tagged *mfg1Δ* strain and a



**Fig. 1.** (A) (Top) Haploid invasive growth mutants after plate wash and regrowth; (bottom) distribution of quantitative phenotypes. Mutants with a phenotypic score  $\leq -0.7$  or  $\geq 0.7$  were classified as hypoinvasive or hyperinvasive, respectively (18). (B) (Top) Pseudohyphal growth mutants after 5 days growth on SLAD medium; (bottom) distribution of quantitative pseudohyphal growth phenotypes. Mutants with scores  $\leq -7$  were classified as hypopseudohyphal, whereas scores  $\geq 10$  were considered to have

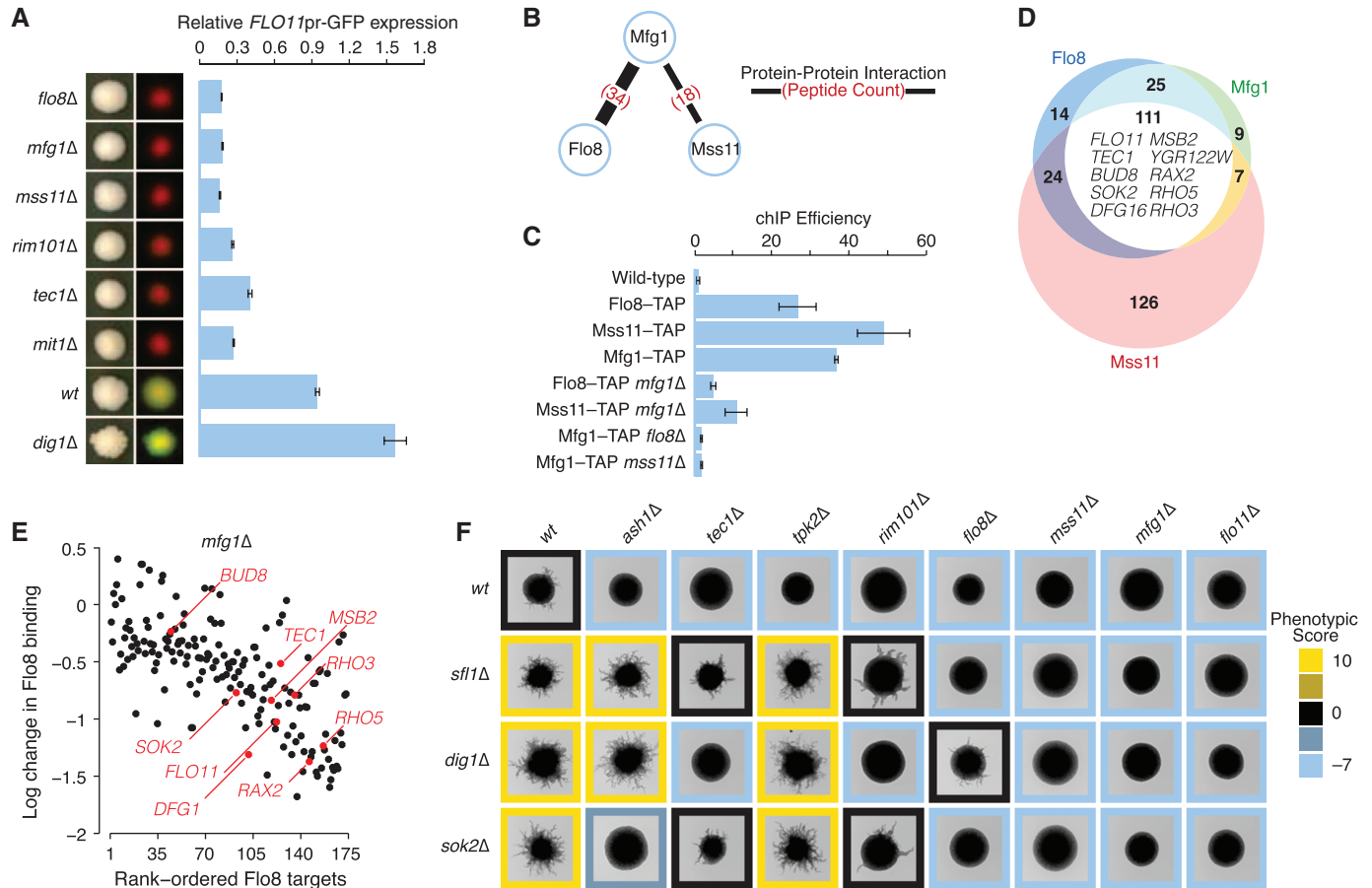
a hyperpseudohyphal phenotype (18). (C) (Top) Biofilm mat-forming mutants after 5 days growth on 0.3% agar; (bottom) distribution of quantitative biofilm formation phenotypes. Mutants with scores  $\leq -26$  were classified as hypobiofilm, whereas scores  $\geq 26$  were considered to have a biofilm formation phenotype (18). The fraction of mutants with hypoactive phenotypic scores is shown in blue, and the fraction of mutants with hyperactive scores is shown in yellow.



**Fig. 2.** Venn diagram of the total number of mutants tested in all three phenotypic assays that showed significant dimorphism phenotypes. Examples of core genes required for all three phenotypes and polyamine biosynthetic genes required specifically for pseudohyphal growth are highlighted.

Mfg1-tagged *flo8Δ* strain, such that the tagged protein is assessed for target binding in the absence of the other transcription factor (table S7), and found that the global fraction of target genes that showed reduced binding were 98.6% and 90.8% of those identified for Mfg1 (Fig. 3E) and Flo8 (fig. S6), respectively.

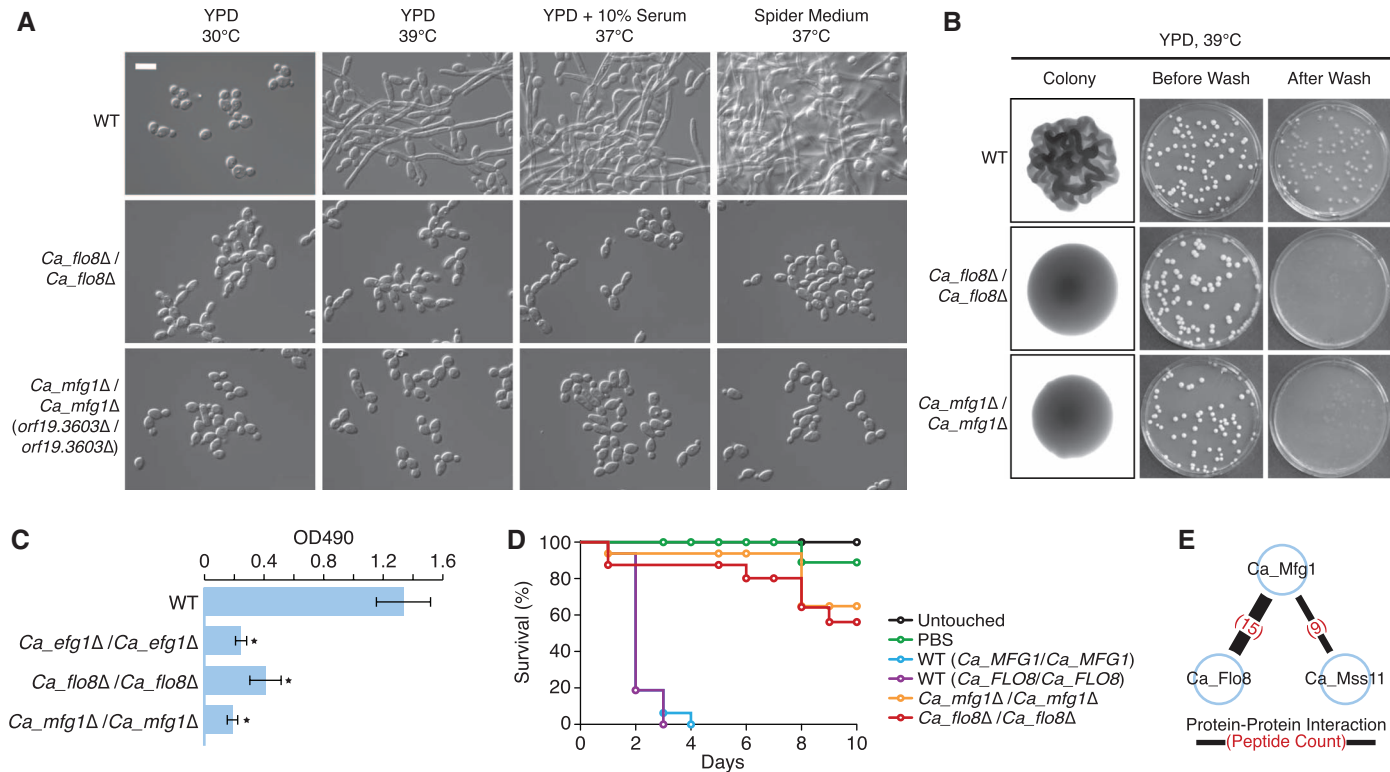
To assess the extent to which Mfg1 contributes to *FLO11* expression, we examined pseudohyphal growth in double mutants. We combined deletion alleles that are defective for negative regulators of *FLO11* expression, including *sfl1Δ*, *dig1Δ*, and *sok2Δ*, with deletion alleles of signaling molecules and transcriptional activators that control *FLO11* expression. This generated a double-mutant epistasis profile for each of the deletion alleles and revealed that *mfg1Δ* and *mss11Δ* suppress the hyperfilamentation phenotypes associated with each of the three negative regulators (Fig. 3F). Thus, Mfg1 appears to function like Mss11 as a critical regulator of filamentous growth.



**Fig. 3.** (A) Expression of *FLO11pr*-GFP relative to *RPL39B-RFP* in haploid deletion mutants grown for 4 days on 2% agar. (B) Mfg1 physically interacts with Flo8 and Mss11 in  $\Sigma$ 1278b cells as determined by coimmunoprecipitation coupled with mass spectrometry. (C) ChIP of Mfg1, Mss11, and Flo8 at  $\sim$ 1.1 kb of the *FLO11* promoter. Error bars indicate SEM. (D) Venn diagram depicts the overlap of promoter enrichment by Mfg1, Mss11, and Flo8 assessed by calling-card analysis. (E) Decreased levels of Flo8 target gene interactions as measured

by calling-card analysis in *mfg1Δ* mutant versus wild-type cells. (F) Double homozygous diploid mutant phenotypes for genes that affected pseudohyphal growth. Single mutants annotated with a hyperfilamentous phenotype are listed on the vertical axis, and single mutants annotated with a hypofilamentous phenotype are on the horizontal axis. Double mutants exhibiting no, a hypofilamentous, or a hyperfilamentous phenotype relative to the single mutant control are highlighted by black, blue, and yellow squares, respectively.





**Fig. 4. (A)** Morphology of cells grown in liquid yeast extract, peptone, and dextrose medium (YPD) at 30°C for 8 hours or under different filament-inducing conditions, as indicated. **(B)** Cells were plated on YPD agar and grown at 39°C for 5 days to assess colony morphology. **(C)** Biofilms were grown in standard *C. albicans* RPMI growth conditions, and metabolic activity was quantified. Error bars indicate SEM. **(D)** Virulence of indicated *C. albicans* strains was tested in a *G. mellonella* survival model of pathogenesis. **(E)** Ca\_Mfg1 physically interacts with Ca\_Flo8 and Ca\_Mss11 in *C. albicans* cells as determined by coimmunoprecipitation coupled with mass spectrometry.

If *MFG1* is a conserved regulator of filamentous growth, then the orthologous gene encoding a similar protein in *C. albicans* should have a role in dimorphism and pathogenicity. The previously uncharacterized gene *Ca\_MFG1* (*orf19.3603*) is the ortholog of *S. cerevisiae* *MFG1* but was absent from the examined *C. albicans* mutant libraries. Deletion of *Ca\_MFG1* blocked filamentation and invasive growth in response to numerous environmental cues, similar to deletion of *Ca\_FLO8* (Fig. 4A, B). The homozygous diploid *Ca\_mfg1Δ / Ca\_mfg1Δ* deletion mutant was also defective in the formation of biofilms (Fig. 4D), resembling the phenotype of mutants lacking *Ca\_FLO8* or *Ca\_EFG1* (Fig. 4C), both of which are known to be critical for this process (6). Consistent with the importance of morphogenetic plasticity for virulence, the *Ca\_mfg1Δ / Ca\_mfg1Δ* mutant had decreased virulence in the greater wax moth *Galleria mellonella* infection model (Fig. 4D). Complementation of the *Ca\_mfg1Δ / Ca\_mfg1Δ* mutant with a wild-type *Ca\_MFG1* allele restored wild-type phenotypes (fig. S7). Lastly, we analyzed Ca\_Mfg1 protein interactions and found that Ca\_Mfg1 physically interacts with Ca\_Flo8 and Ca\_Mss11 (Fig. 4E and tables S8 and S9). These findings highlight conserved cellular circuitry controlling filamentous growth and identify Ca\_Mfg1 as a previously unknown component of the *C. albicans* Flo8-Mss11 complex, which is integral for filamentous morphogenesis (23, 24). We conclude that

systematic genetic analyses of diverse *S. cerevisiae* strains provides a powerful and general approach to identify not only the function of previously uncharacterized genes within this model system but also the function of orthologous genes across distantly related yeast strains, including our understanding of filamentation in fungal pathogens.

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**Acknowledgments:** We thank M. Johnston for inspiring the calling-card analysis and M. Usaj for assistance with image and data processing. Supported by the Canadian Institutes of Health Research (MOP-97939) (C.B. and B.A.), Natural Sciences and Engineering Research Council (NSERC) of Canada (RGPIN 204899-05) (C.B.), Howard Hughes Medical Institute Research Scholar (C.B.), Career Award in the Biomedical Sciences from the Burroughs Wellcome Fund (L.E.C.), Canada Research Chair in Microbial Genomics and Infectious Disease (L.E.C.), NSERC Discovery Grant (355965-2009) (L.E.C.), and NIH (GM40266 and GM035010) (G.R.F.). C.N. and G.G. are supported by a grant from the National Human Genome Research Institute. R.S.S. is supported by an NSERC Canada Graduate Scholarship. C.F.K. is supported by a European Molecular Biology Organization long-term fellowship. Raw images and data derived from haploid invasive growth, pseudohyphal growth and biofilm formation assays can be downloaded from [http://spidey.ccr.utoronto.ca/data/ryan\\_et\\_al/](http://spidey.ccr.utoronto.ca/data/ryan_et_al/).

**Supplementary Materials**  
[www.sciencemag.org/cgi/content/full/337/6100/1353/DC1](http://www.sciencemag.org/cgi/content/full/337/6100/1353/DC1)  
Materials and Methods  
Figs. S1 to S7  
References (25–41)  
7 May 2012; accepted 16 July 2012  
10.1126/science.1224339

# A Critical Period for Social Experience–Dependent Oligodendrocyte Maturation and Myelination

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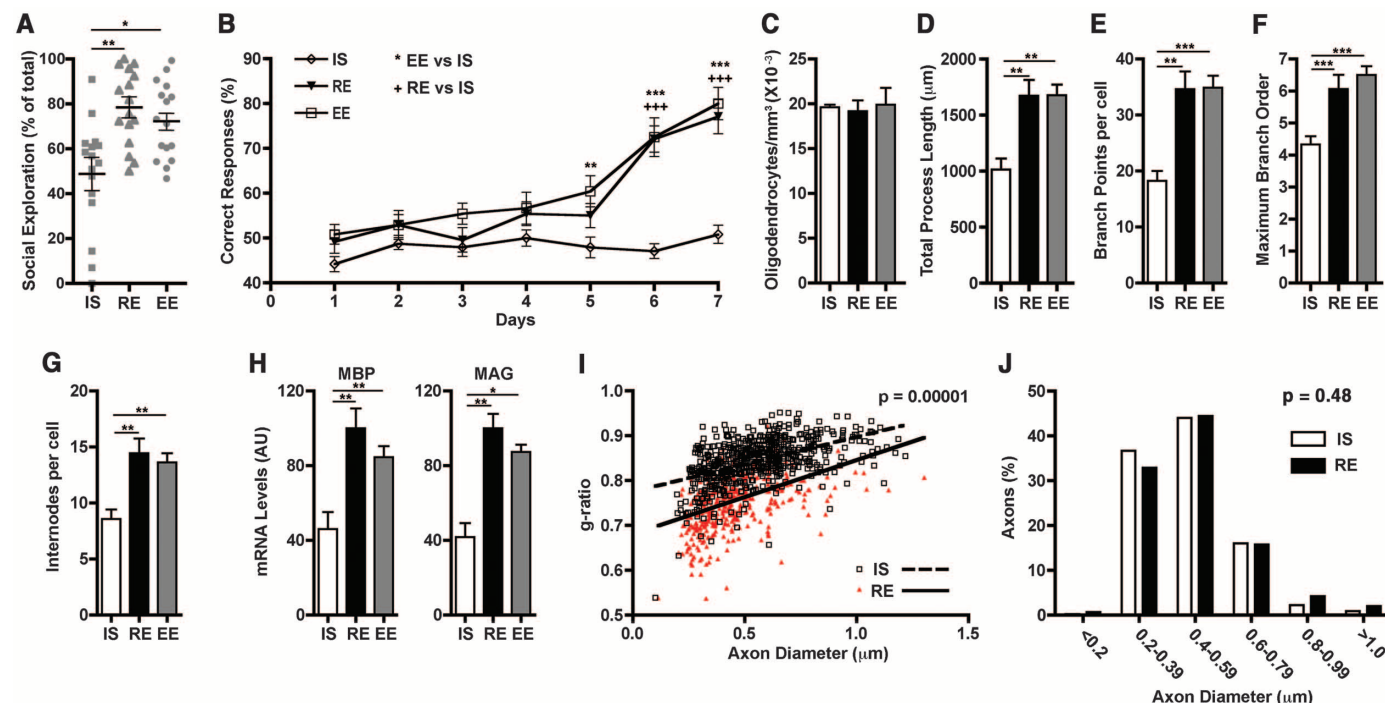
Early social isolation results in adult behavioral and cognitive dysfunction that correlates with white matter alterations. However, how social deprivation influences myelination and the significance of these myelin defects in the adult remained undefined. We show that mice isolated for 2 weeks immediately after weaning have alterations in prefrontal cortex function and myelination that do not recover with reintroduction into a social environment. These alterations, which occur only during this critical period, are phenocopied by loss of oligodendrocyte ErbB3 receptors, and social isolation leads to reduced expression of the ErbB3 ligand neuregulin-1. These findings indicate that social experience regulates prefrontal cortex myelination through neuregulin-1/ErbB3 signaling and that this is essential for normal cognitive function, thus providing a cellular and molecular context to understand the consequences of social isolation.

Juvenile social isolation and neglect influence adult cognitive function and social interactions (1–4). Studies of children raised

in institutions where neglect was rampant showed that deprivation also correlates with alterations in white matter tracts associated with the medial prefrontal cortex (mPFC), which are not reversed by subsequent foster care placement (5, 6). Similarly, rhesus monkeys isolated as juveniles have white matter disturbances and impaired working memory in adulthood (7), suggesting that juvenile social experience and forebrain white matter development are linked. Studies indicate that experience and neuronal activity influence central

nervous system (CNS) myelin (8). However, it remains unclear whether any effect of social experience on oligodendrocytes is important for the establishment of normal adult neuronal circuits and their function, what aspects of oligodendrocyte development are regulated by social experience, and which molecular mechanisms underlie these events. To explore the effects of juvenile social experience on CNS myelination and function, we focused on the murine mPFC.

Male mice expressing enhanced green fluorescent protein in oligodendrocytes under the control of the proteolipid protein (PLP) promoter (PLP-eGFP) (9, 10) were housed under one of the following conditions beginning at weaning [postnatal day 21 (P21)]: in isolation (IS, single mouse per standard cage), in a regular environment (RE, four mice per standard cage), or in an enriched environment (EE, large cage with eight mice and novel toys replaced every 48 hours). To determine whether these environments affected mPFC function, 4 weeks later (P50), we tested two mPFC-dependent behaviors, sociability [using a social interaction test; (11)] and working memory [using a nonmatching-to-place task; (12)]. Only isolated animals showed alterations, with decreases in both social interaction and acquisition in the nonmatching-to-place task (Fig. 1, A and B). General locomotive activity was not altered in isolated mice (fig. S1), which indicated that the change in social behavior was specific. In contrast, as previously described (13),



**Fig. 1.** PFC-dependent behaviors and mPFC oligodendrocytes are altered by juvenile isolation. (A and B) Mice reared in isolation starting at P21 (IS), by P50 show alterations in social interactions (A) and working memory (B) compared with mice in regular (RE) or enriched environment (EE) ( $n = 16$  mice per group). (C to G) Rearing environment does not influence mPFC oligodendrocyte density by P65 ( $n = 3$  mice per group), but social isolation results

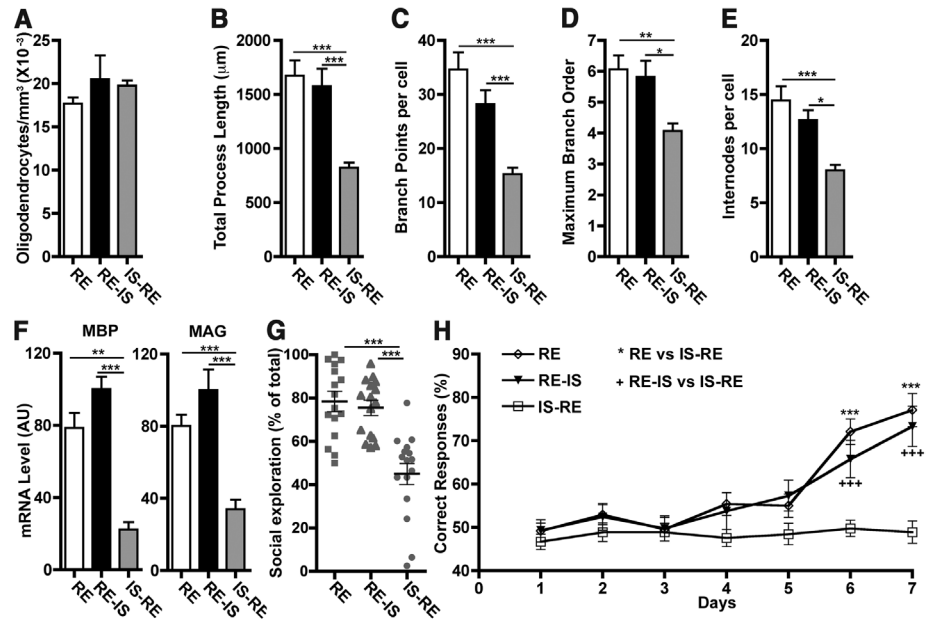
in mPFC oligodendrocytes with simpler morphology (cells per condition: IS = 12, RE = 16, EE = 16). (H) P21 to P65 isolation reduces mPFC MBP and MAG expression. AU = arbitrary units; (mice per group: IS = 8, RE = 8, EE = 4). (I to J) P21 to P65 isolation leads to reduced mPFC myelin thickness ( $n = 3$  per group) without changes in axon diameters (450 axons per group). \* $P < 0.05$ , \*\* $P < 0.01$ , \*\*\* $P < 0.001$ . Error bars, SEM.

locomotive activity was reduced in animals raised in an enriched environment.

Then, mPFC myelination was analyzed at P65. The density of mPFC oligodendrocytes was the same in all groups (Fig. 1C), and oligodendrocyte morphology was indistinguishable between mice raised in enriched or regular environments (Fig. 1, D to G). However, the morphology of mPFC oligodendrocytes from isolated mice was markedly simpler, with shorter processes, less branching, and fewer internodes (Fig. 1, D to G). Furthermore, mPFC expression of two myelin genes, myelin basic protein (MBP) and myelin-associated glycoprotein (MAG), was reduced in isolated mice (Fig. 1H). Additionally, electron microscopy showed that isolated mice had reduced mPFC myelin thickness, whereas myelinated axon diameter was unaffected (Fig. 1, I and J). Thus, social isolation from weaning to sexual maturity, which interferes with the elaboration of mPFC-dependent behaviors (14, 15), also alters mPFC myelination and yields oligodendrocytes with simpler morphologies.

To determine when social experience influences mPFC myelination most, we examined oligodendrocytes in mice housed under regular conditions (RE) and found that P21 to P35 is a period of significant mPFC oligodendrocyte maturation (fig. S2). Further analysis at P35 showed that mice exposed to just 2 weeks of isolation (P21 to P35) exhibited deficits similar to those seen in mice isolated from P21 to P65 (fig. S3). Therefore, we wondered whether P21 to P35 is a critical period for the influence of social isolation on myelination. When isolation was initiated after P35 (RE-IS), oligodendrocyte morphology and myelin gene expression were indistinguishable from those in normally reared mice by P65 (Fig. 2, A to F). In contrast, if mice were isolated from P21 to P35 and then returned to regular housing until P65 (IS-RE), oligodendrocytes displayed abnormal morphology (Fig. 2, A to F). Behavioral tests showed similar results: Mice isolated for 2 weeks immediately after weaning and then returned to regular housing (IS-RE) displayed deficits equivalent to those seen in mice isolated P21 to P65, whereas mice isolated only P35 to P65 (RE-IS) performed like regularly housed mice (RE) (Fig. 2, G and H, and fig. S1B). Thus, social isolation from P21 to P35 alters mPFC oligodendrocyte morphology, myelination, and mPFC-mediated behaviors. These effects persist even when isolated mice are re-exposed to social interactions, which suggests a link between the quality of mPFC myelination established during the juvenile period and adult behaviors.

The effects of juvenile social experience likely occur because of changes in signaling pathways important for oligodendrocyte maturation such as neuregulin-1-ErbB (NRG1-ErbB) (16–22). Although there has been some controversy surrounding the role of this signaling pathway in CNS myelination (23, 24), oligodendrocytes express the ErbB2 and ErbB3 receptors (16, 23),



**Fig. 2.** The effects of social isolation on mPFC oligodendrocytes and PFC-dependent behaviors occur only during a critical period and are not reversed by reintroduction to a social environment. (A to E) mPFC oligodendrocytes show morphological alterations in mice isolated P21 to P35 and then returned to regular environment until P65 (IS-RE), but not in mice housed in regular environment until P35 and isolated thereafter (RE-IS). Early social isolation does not affect oligodendrocyte density ( $n = 3$  mice per group), but does alter morphology (cells per group: RE = 16, RE-IS = 11, IS-RE = 14). (F) IS-RE mice showed reductions in mPFC MBP and MAG expression ( $n = 8$  mice per group) and alterations in (G) sociability and (H) working memory ( $n = 16$  mice per group). \* $P < 0.05$ , \*\* $P < 0.01$ , \*\*\* $P < 0.001$ . Error bars, SEM.

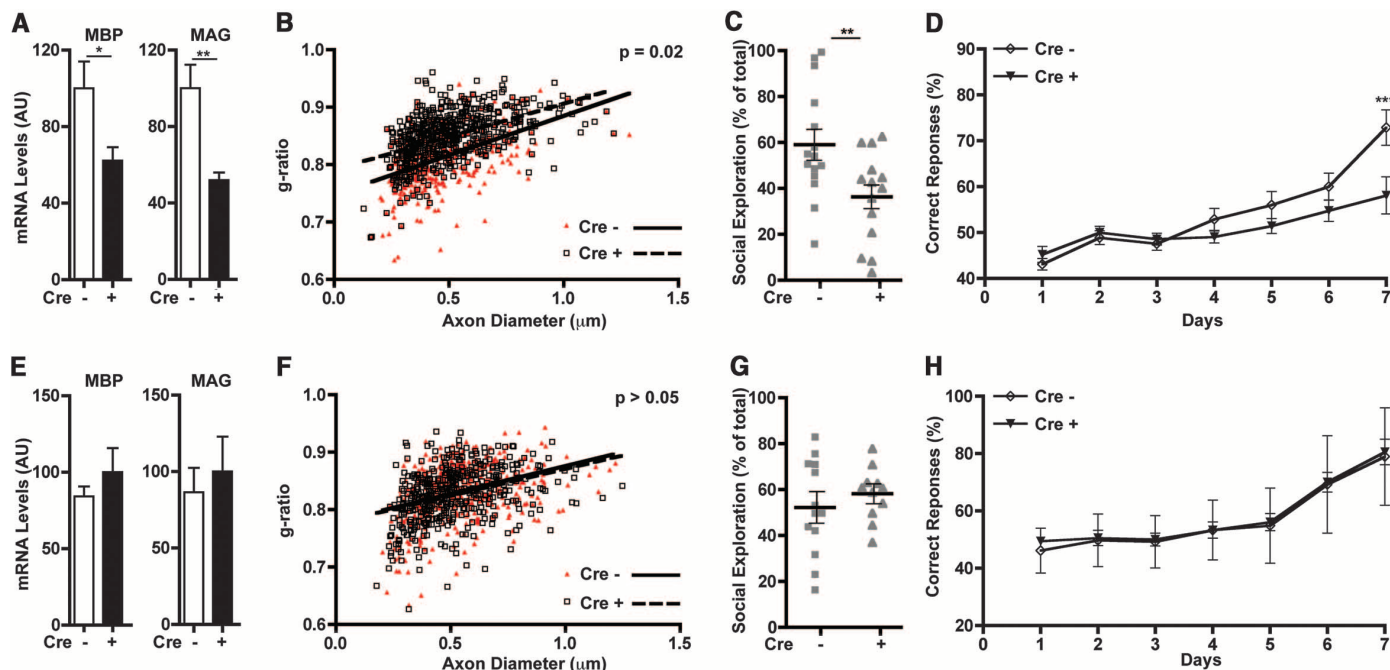
and hypomyelination occurs in mice with reduced oligodendrocyte ErbB signaling or NRG1 expression (21, 22). To directly explore the link between ErbB signaling in oligodendrocytes and mPFC myelination in response to isolation, we generated mice with an inducible oligodendrocyte-specific knockout (KO) of ErbB3 using mice carrying an ErbB3 floxed allele (25) and mice expressing the tamoxifen-inducible Cre recombinase (CreERT) under the control of the PLP promoter (PLP/CreERT) (26).

We first tested if ErbB3 could be knocked out in postnatal oligodendrocytes and if this alters myelination in the corpus callosum and the optic nerve. Quantitative reverse transcription fluorescent polymerase chain reaction (qRT-PCR) showed that, when tamoxifen treatment was initiated at P10, by P40 ErbB3 expression in these two regions was reduced by more than 60% in PLP/CreERT::ErbB3floxed/floxed compared with control (ErbB3floxed/floxed) mice (fig. S4, A and C). Furthermore, at this age, PLP/CreERT::ErbB3floxed/floxed mice also had thinner myelin in both structures (fig. S4, B, D, E and F) without changes in axon caliber (fig. S4, G and H), which proved that ErbB3 signaling in oligodendrocytes after P10 is necessary for the generation of myelin of the correct thickness in white matter tracts of the brain. Next, we tested the impact of loss of ErbB3 in oligodendrocytes during the critical period for mPFC myelination and function. Using qRT-PCR, we confirmed that ErbB3 mPFC expression was knocked down whether tamoxifen

injections were initiated before or after the critical period, i.e., P19 or P36 (fig. S5). Then, cohorts of PLP/CreERT::ErbB3floxed/floxed and ErbB3floxed/floxed mice housed under regular conditions (RE) received tamoxifen injections beginning at either P19 or P36 and were analyzed between P50 and P65. Mice that lost oligodendrocyte ErbB3 expression starting at P19 phenocopied socially isolated wild types; i.e. they exhibited reduced myelin gene expression (Fig. 3A), reduced myelin thickness in mPFC (Fig. 3B), and alterations in sociability and working memory (Fig. 3, C and D, and fig. S1C). In contrast, ablation of oligodendrocyte ErbB3 from P36 onward had no effect on MBP and MAG (Fig. 3E), myelin thickness (Fig. 3F), or mPFC-dependent behaviors (Fig. 3, G and H, and fig. S1C). Thus, ErbB3 signaling in mPFC oligodendrocytes is only required during the critical period to achieve normal myelination, and in its absence, mPFC-dependent behaviors are abnormal.

To further investigate the involvement of ErbB signaling in mPFC myelination, we used mice expressing a dominant-negative ErbB4 receptor (DN-ErbB4) in oligodendrocytes under the control of the promoter for 2',3'-cyclic nucleotide 3'-phosphodiesterase (CNP-DN-ErbB4::PLP-eGFP mice) (21). DN-ErbB4 interferes specifically with ErbB3 and ErbB4 signaling (18, 21, 27). CNP-DN-ErbB4 mice housed in a regular or an enriched environment displayed oligodendrocytic and behavioral phenotypes similar to those of wild types reared in social isolation during the critical period (fig. S6). Thus, interfering with

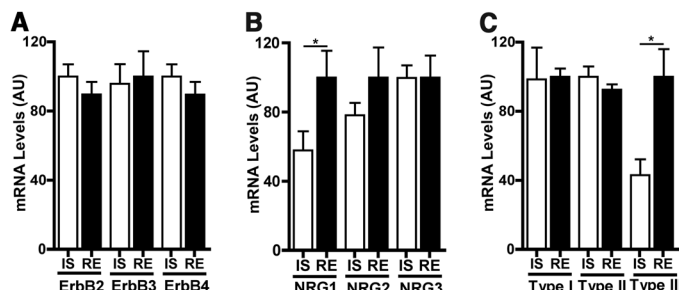




**Fig. 3.** Loss of ErbB3 signaling in oligodendrocytes during the critical period for myelination mimics the effects of social isolation. (**A** to **D**) When Cre-mediated ErbB3 knockdown in oligodendrocytes begins at P19 (Cre+), by P65 mice have (**A**) reduced mPFC MBP and MAG expression ( $n = 7$  per group); (**B**) reduced myelin thickness (Cre-;  $n = 3$ , Cre+;  $n = 4$ ), (**C**) altered sociability,

and (**D**) altered working memory (Cre-;  $n = 15$ , Cre+;  $n = 14$ ). (**E** to **H**) No effects were observed when tamoxifen was injected starting at P36 (mRNA measurement: Cre-;  $n = 4$ , Cre+;  $n = 5$ ; myelin thickness:  $n = 3$  for, behavioral tests: Cre-;  $n = 13$ , Cre+;  $n = 12$ ).  $*P < 0.05$ ,  $**P < 0.01$ ,  $***P < 0.001$ . Error bars, SEM.

**Fig. 4.** Social isolation alters mPFC type III NRG1 expression. (**A** and **B**) Isolation from P21 to P35 (IS) did not change mPFC expression levels of ErbB2, ErbB3, and ErbB4 but reduced NRG1 mRNA levels. (**C**) Isoform specific qRT-PCR showed that the effect of isolation was limited to type III NRG1 ( $n = 8$  per group).  $*P < 0.05$ . Error bars, SEM.



oligodendrocyte ErbB signaling eliminates the positive effects of social experience on mPFC myelination and development of normal behavior.

To test if mPFC NRG1-ErbB signaling is regulated by juvenile social experience, we compared the levels of expression of components of this pathway between mice isolated P21 to P35 and those in regular housing. Isolation did not change expression of ErbB2, ErbB3, ErbB4, NRG2, or NRG3 (Fig. 4, A and B). However, isolated mice showed a significant decrease in expression of the epidermal growth factor-like domain of NRG1, common to all NRG1 isoforms (28) (Fig. 4B). The *Nrg1* gene produces numerous isoforms through alternative splicing and the activity of several promoters (28). The decrease in NRG1 expression was limited to type III NRG1 (Fig. 4C), the isoform most highly expressed in the mPFC (fig. S7). mPFC type III NRG1 mRNA levels in isolated mice were lower at P35 than at P21 (fig.

S8A), and isolation resulted in reduced mPFC NRG1 expression in CNP-DN-ErbB4 mice (fig. S8B), showing that isolation reduces mPFC type III NRG1 expression independently of oligodendrocyte ErbB signaling.

Our results demonstrate that juvenile social experience influences oligodendrocyte maturation and myelination in the murine mPFC during a temporally restricted “critical period” between P21 and P35. This effect depends on oligodendrocyte ErbB3 signaling. Note that mice in which oligodendrocyte maturation and/or myelination is abnormal because of loss of ErbB3 signaling phenocopy the behaviors elicited by social isolation during the critical period, which indicates that experience-dependent oligodendrocyte maturation is necessary for normal social behavior and working memory in the adult. At the same time, the motor cortex, a region adjacent to mPFC, showed none of the social experience-dependent

changes in gene expression observed in the mPFC (fig. S9), which highlights the specificity of the effects of social experience.

How do myelin defects produce these behavioral and/or cognitive deficiencies? One scenario is that thinner myelin changes conduction velocity of myelinated mPFC axons, which leads to abnormal information processing, which in turn contributes to the aberrant social behaviors and working memory. Also, loss of oligodendrocyte ErbB signaling by DN-ErbB4 produces changes in dopamine neurotransmission similar to those generated by juvenile isolation (21, 29). Thus, a second possibility is that myelin defects caused by isolation change dopaminergic function, which contributes to the deficits in working memory and social interactions (30, 31). Although the changes in NRG1 expression induced by isolation might also modify ErbB4 signaling in interneurons (32), because elimination of ErbB3 signaling in oligodendrocytes phenocopies isolation, it is evident that oligodendrocyte ErbB3 signaling is essential in this context.

There is consensus that NRG1-ErbB signaling plays a central role in peripheral nervous system myelination (18–20, 24), but its roles in the CNS were controversial. It is now apparent that ErbB signaling is not required for the initiation of CNS myelination, but that ErbB3 is necessary for late events in oligodendrocyte maturation and myelination; i.e., oligodendrocyte ErbB3 and ErbB4 loss does not produce myelin defects by P11 (24), but loss of oligodendrocyte ErbB3 starting at P10 causes hypomyelination in the

corpus callosum and optic nerve. Furthermore, in the mPFC, hypomyelination occurs even when oligodendrocyte ErbB3 is lost at later stages (after P19). Moreover, mPFC myelination in CNP-DN-ErbB4 mice is not different from wild type at P21 but is clearly altered by P35 (fig. S10). ErbB4 KO mice do not have alterations in CNS myelin even upon reaching adulthood (24), and loss of ErbB3 produces the same phenotype as expression of DN-ErbB4, which blocks both ErbB3 and ErbB4 function; this indicates that ErbB3 is the critical ErbB receptor for CNS myelination. Our data suggest that normal type III NRG1 expression is necessary for mature mPFC myelination, in agreement with the observation that reduced type III NRG1 expression leads to hypomyelination in several brain regions (22), whereas NRG1 overexpression results in thicker CNS myelin (24).

The effects of social experience on mPFC myelination depend, at least in part, on the social experience-dependent regulation of NRG1-ErbB3 signaling. We propose that lack of social interactions during the juvenile period leads to reduced type III NRG1 expression by mPFC neurons, resulting in reduced oligodendrocyte ErbB3 signaling and thus incomplete oligodendrocyte maturation and myelination. Previous studies showed that neuronal activity influences expression of type I but not type III NRG1 mRNA in the intact brain and cultures of cortical neurons (33), a finding we replicated in primary cultures of frontal cortex neurons (fig. S11A). Furthermore, expression of type III NRG1 was unaffected in the mPFC of mice with oligodendrocyte ErbB3 KO or those expressing DN-ErbB4 in oligodendrocytes (fig. S11B). These results suggest that social experience affects mPFC myelination by influencing the levels of type III NRG1 in mPFC neurons independent of neuronal depolarization and ErbB receptor signaling in oligodendrocytes. Nevertheless, the possibility that other molecular events also contribute to the effects of social experience on myelination should not be dismissed. For example, *in vitro* studies by Wake *et al.* (34) showed that release of glutamate along axons induces myelination in part by increasing synthesis of myelin proteins in the associated oligodendrocytes. Thus, electrical activity in mPFC might influence the translation of mRNA species that are regulated by type III NRG1 in an experience-dependent fashion and so contribute to normal myelination.

Our findings indicate that the effects of childhood isolation and neglect on adult mental health might be caused, at least in part, by alterations in oligodendrocytes and myelin development. Furthermore, we provide a cellular and/or molecular context and genetic models in which to begin to understand the effects of juvenile social experience on brain development in general and myelin maturation in particular. Our results also may be relevant to neuropsychiatric disorders such as schizophrenia and mood disorders, which usually manifest after the juvenile period and have been linked to alterations in white matter and myeli-

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Figs. S1 to S11

Table S1

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21 February 2012; accepted 13 July 2012

10.1126/science.1220845

## Active DNA Demethylation in Plant Companion Cells Reinforces Transposon Methylation in Gametes

Christian A. Ibarra,<sup>1\*</sup> Xiaoqi Feng,<sup>1\*</sup> Vera K. Schoft,<sup>2\*</sup> Tzung-Fu Hsieh,<sup>1\*</sup> Rie Uzawa,<sup>1</sup> Jessica A. Rodrigues,<sup>1</sup> Assaf Zemach,<sup>1</sup> Nina Chumak,<sup>2</sup> Adriana Machlicova,<sup>2</sup> Toshiro Nishimura,<sup>1</sup> Denisse Rojas,<sup>1</sup> Robert L. Fischer,<sup>1†</sup> Hisashi Tamaru,<sup>2†</sup> Daniel Zilberman<sup>1†</sup>

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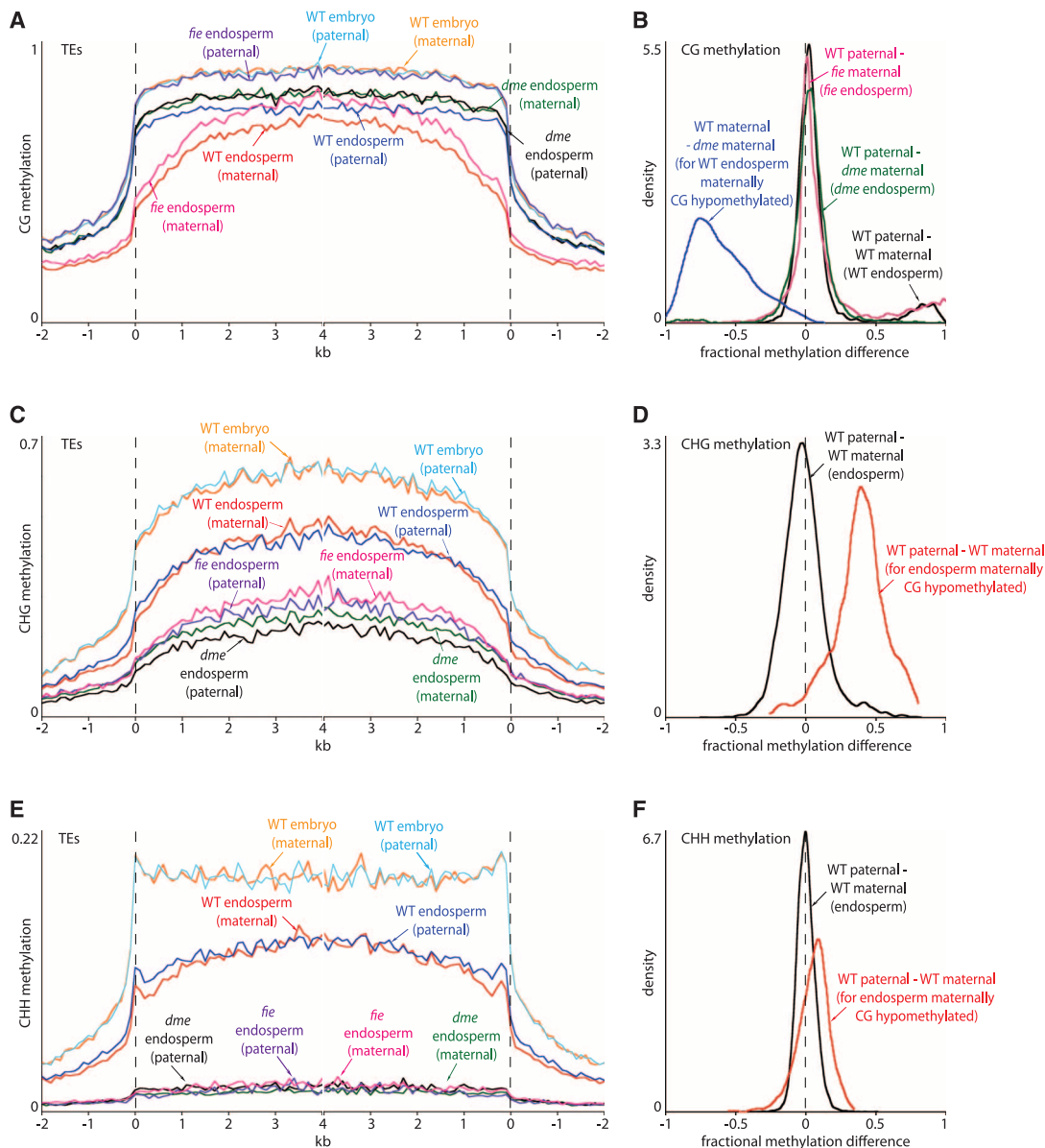
Flowering plant sexual reproduction involves two fertilization events (2). The pollen vegetative cell forms a tube that carries two sperm cells to the ovule, where one fuses with the diploid central cell to form the triploid placenta-like endosperm, and the other fertilizes the haploid egg to produce the embryo. Endosperm DNA of *Arabidopsis thaliana* is modestly, but globally, less methylated than embryo DNA in all contexts (3). The DEMETER (DME) DNA glycosylase that excises 5-methylcytosine is highly expressed in the central cell before fertilization and is at least partially required for the demethylation ob-

served in endosperm (2, 3), which has been inferred to occur on the maternal chromosomes inherited from the central cell. Passive mechanisms, such as down-regulation of the MET1 DNA methyltransferase, have also been proposed to contribute to demethylation of the maternal endosperm genome (2). The global differences between embryo and endosperm are consistent with passive demethylation and suggest that the process may have little sequence specificity (3, 4). However, DNA methylation of the maternal and paternal endosperm genomes has not been compared except for a few loci, and therefore, it is difficult to make general inferences about the mechanism and specificity of central cell demethylation. Why the central cell should undergo extensive DNA demethylation is also unclear.

To understand the extent, mechanism, and biological significance of active demethylation in the central cell, we used reciprocal crosses between

the Col and *Ler* accessions of *Arabidopsis* that differ by >400,000 single-nucleotide polymorphisms (SNPs) (4) to identify DNA methylation that resides on either the maternal or paternal endosperm genome (5) by shotgun bisulfite sequencing (table S1). The wild-type maternal genome is substantially less methylated than the paternal genome in the CG context (Fig. 1A and figs. S1 and S2), with slight global hypomethylation accompanied by strong local demethylation (Fig. 1B and figs. S3 and S4). The local demethylation is nearly fully reversed in *dme* mutant endosperm (Fig. 1, A and B, and figs. S2, S4, and S5), which indicates that DME is either the only or by far the major enzyme required for excision of 5-methylcytosine in the central cell and demonstrating that active DNA demethylation of at least 9816 specific sequences spanning 4,443,250 bp (table S2) accounts for the methylation differences between the maternal and paternal endosperm

**Fig. 1.** Local DME-dependent demethylation of maternal endosperm chromosomes. (A, C, and E) Transposons were aligned at the 5' and 3' ends (dashed lines) and average methylation levels for each 100-bp interval are plotted. (B, D, and F) Kernel density plots trace the frequency distribution of endosperm methylation differences for all 50-bp windows with an informative SNP. A shift of the peak with respect to zero represents a global difference; shoulders represent local differences.



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genomes. Global CG methylation of both maternal and paternal genomes is slightly elevated by lack of DME compared with wild type (Fig. 1A and fig. S5), consistent with overexpression of genes that mediate CG methylation in *dme* endosperm (4).

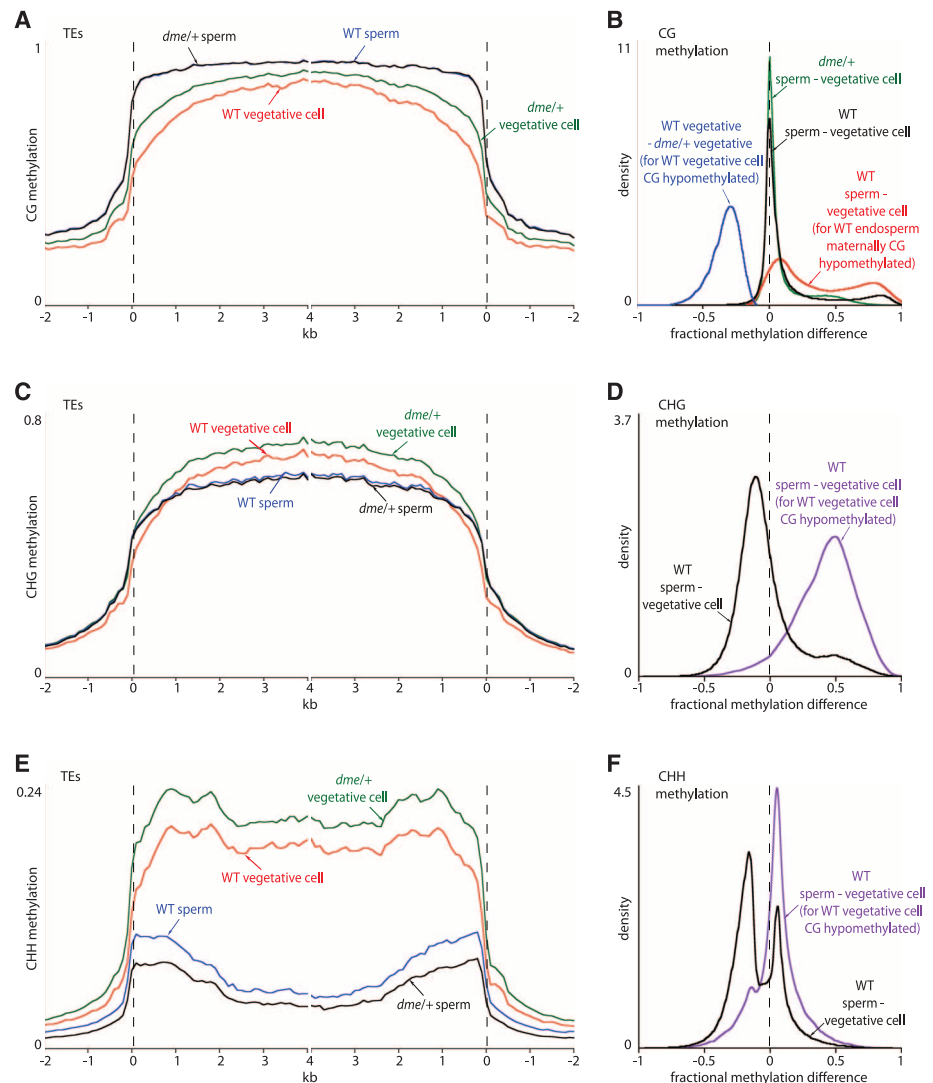
Global CHG methylation of the wild-type endosperm maternal genome is similar to that of the paternal genome (Fig. 1, C and D), but loci that are maternally demethylated in the CG context show strong maternal CHG demethylation (Fig. 1D), consistent with the reported in vitro activity of DME on methylation in all sequence contexts (6). A similar but weaker correspondence exists for CHH methylation (Fig. 1, E and F), presumably because sRNA-directed DNA methylation (RdDM) patterns are more variable, and may be partially restored after fertilization. We did not observe major methylation differences between parental genomes in embryo (Fig. 1, A, C, and E; and figs. S1, S2, S4, and S6).

As we showed previously, *dme* endosperm has greatly reduced CHG methylation and almost no CHH methylation (3), and our present data show that this applies similarly to both parental genomes (Fig. 1, C and E, and fig. S2). As this is the opposite of the outcome expected from a mutation in a demethylating enzyme, we hypothesized an indirect mechanism. DME activity is required for functionality of the Polycomb repressive complex 2 (PRC2) in endosperm, prompting us to examine methylation in endosperm lacking maternal activity of the core PRC2 protein FIE (2). Lack of FIE had an effect similar to that of lack of DME on non-CG methylation (Fig. 1, C and E, and table S1), which indicates that PRC2 promotes non-CG DNA methylation in endosperm. In contrast, local maternal CG demethylation was mostly unaffected by lack of FIE (Fig. 1B and figs. S4 and S5), as would be expected with direct activity of DME. Global CG methylation levels were increased even more than in *dme* endosperm (Fig. 1A and fig. S5), consistent with strong overexpression of genes that mediate CG methylation in *fie* endosperm (4).

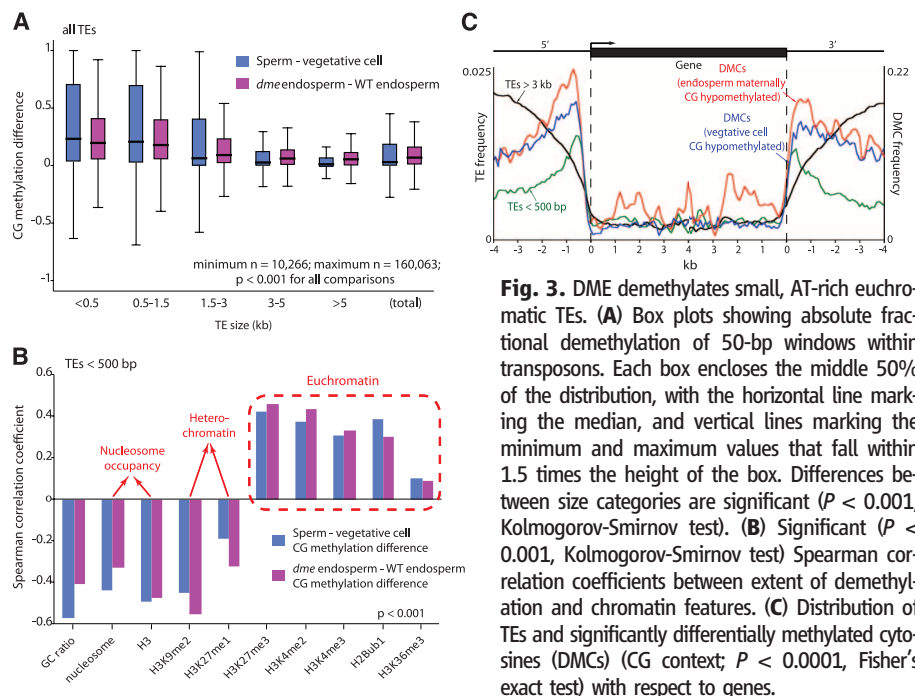
DME-mediated DNA demethylation in the central cell is required to establish monoallelic (imprinted) expression of a number of genes in the endosperm (2, 4). We examined the location of loci that are significantly less methylated in wild-type endosperm than in *dme* endosperm (table S2) in relation to imprinted endosperm genes (fig. S4). Maternally and paternally expressed genes are preferentially associated with such differentially methylated regions (DMRs), particularly just upstream of the gene (fig. S7). Maternally expressed genes also exhibit DMRs that span the transcriptional start site (fig. S7), consistent with the strong correlation between methylation of this region and gene silencing (1). Paternally expressed genes are enriched in DMRs within the gene body (fig. S7), which suggests that gene body demethylation can disrupt gene expression, for example, by revealing repressor binding sites, as has been proposed for the DMR downstream of the *PHERES1* gene (fig. S4) (2).

Several TEs were reported to be less methylated in the pollen vegetative cell of *Arabidopsis* compared with sperm (7), and we recently showed that DME is required for demethylation of two genes in the vegetative cell that are demethylated by DME in the central cell (8). These data suggest that DME-mediated DNA demethylation may proceed similarly in the central and vegetative cells. To examine this issue, we compared DNA methylation patterns in sperm and vegetative cell nuclei that were purified by fluorescence-activated cell sorting (8, 9). Most CG sites are heavily and similarly methylated in both cell types, but a subset is specifically demethylated in the vegetative cell (Fig. 2, A and B, and figs. S3, S4, and S8), corresponding to at least 9932 loci spanning 4,068,000 bp (table S2). The demethylated vegetative cell CG sites overlap 45.5% of those demethylated in the maternal endosperm genome and, by extension, in the central cell (Fig. 2B, fig. S4, and table S2).

We examined methylation in pollen from heterozygous *dme*<sup>+/−</sup> plants (strong *dme* alleles cannot be made homozygous), in which half of the pollen lacks DME (8). CG sites that are demethylated in wild-type vegetative cells showed much greater methylation in vegetative cell nuclei isolated from *dme*<sup>+/−</sup> pollen (Fig. 2, A and B, and fig. S4), which indicates that DME is required for demethylation in the vegetative cell. CHG methylation is generally higher in the vegetative cell than in the sperm cell (Fig. 2, C and D), but loci demethylated at CG sites in the vegetative cell are also demethylated at CHG sites (Fig. 2D), as they are in endosperm (Fig. 1D). CHH methylation is very high in the vegetative cell and low in sperm (Fig. 2E), consistent with the strong RdDM activity reported in the vegetative cell (9). Nonetheless, vegetative cell CG-demethylated loci tend to show lower CHH methylation in vegetative cells than in sperm (Fig. 2F). Overall, our data strongly support the hypothesis that DNA demethylation

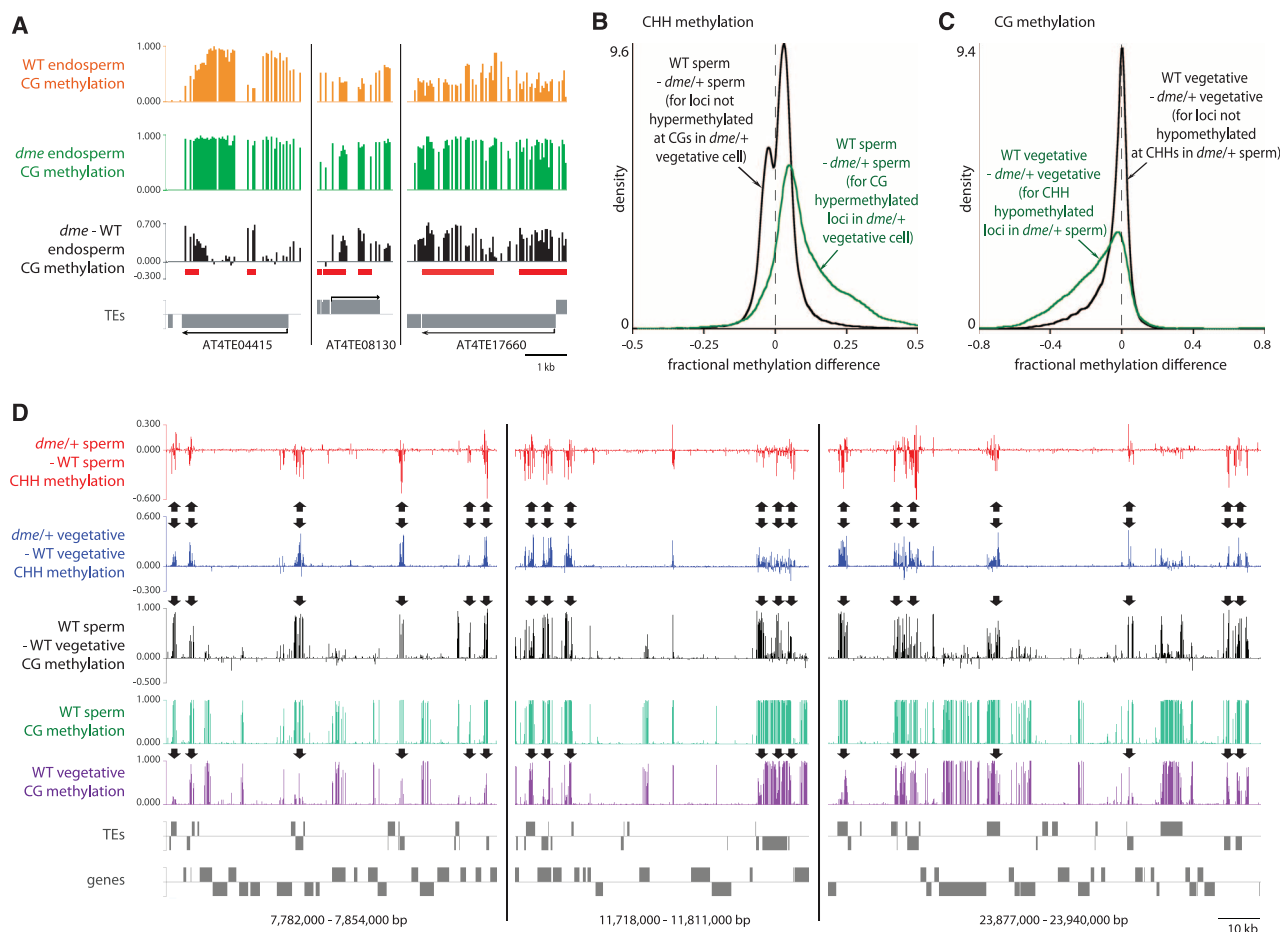


**Fig. 2.** Local DME-dependent demethylation in the pollen vegetative cell. (A, C, and E) Average methylation in transposons was plotted as in Fig. 1. (B, D, and F) Kernel density plots, as in Fig. 1, of pollen methylation differences in 50-bp windows.



in the male and female companion cells proceeds by an active, DME-dependent mechanism.

Loci demethylated in companion cells tend to be within smaller AT-rich TEs that are enriched for euchromatin-associated histone modifications (10) and depleted of nucleosomes with heterochromatin-associated modifications (Fig. 3, A and B, and figs. S9 and S10), which suggests that chromatin structure plays an important role in regulating active DNA demethylation (11), consistent with the decondensation of heterochromatin observed in central and vegetative cells (9, 12). TEs longer than 3 kb are rarely demethylated (Fig. 3A and fig. S3), except at the edges (fig. S9), consistent with our published observations in rice (13). The preference for smaller TE demethylation holds for TEs of various types (fig. S10). Demethylation of small TEs accounts for the shapes of the wild-type maternal endosperm methylation traces (Fig. 1, A, C, and E) and the wild-type vegetative cell methylation traces (Fig. 2, A and C), which are closer to the paternal and sperm traces, respectively, in the middle (long TEs) than at the points of alignment (mostly small TEs). Small *Arabidopsis* TEs, like



**Fig. 4. Demethylation activates TEs in companion cells and reinforces methylation in sperm.** (A) DME-dependent demethylation of TEs that are maternally expressed in wild-type, but not *dme*, endosperm (table S4). DMRs (table S2) are underlined. (B) Kernel density plots of the CHH methylation differences between sperm cells from wild-type and *dme/+* plants. (C) Kernel

density plots of the CG methylation differences between vegetative cells from wild-type and *dme/+* plants. (D) Snapshots of CG and CHH methylation in pollen on chromosome 1. Arrows point out loci with decreased CHH methylation in sperm and increased CG methylation in vegetative cells from *dme/+* pollen.



their rice counterparts (13), tend to occur near genes (Fig. 3C), explaining the observation that DME and related glycosylases preferentially demethylate gene-adjacent sequences (Fig. 3C) (2, 14, 15). This phenomenon explains why CHG and CHH methylation is lower in wild-type vegetative cells compared with sperm near genes (fig. S8), even though overall non-CG methylation is higher in vegetative cells than in sperm (Fig. 2, C to F).

The abundance of DME targets in gene-poor heterochromatin (fig. S11) and the overlap among DME targets in the central and vegetative cells (table S2), despite their different functions and developmental fates, suggest that establishment of genomic imprinting is not the basal function of DME. DNA demethylation and activation of TEs in the vegetative cell was proposed to generate sRNAs that would reinforce silencing of complementary TEs in sperm (7). If such TEs are demethylated in the central cell, their maternal copies should remain active in endosperm. Indeed, we identified 11 TEs demethylated by DME that are specifically maternally expressed in wild-type, but not *dme*, endosperm (Fig. 4A and table S4) (4). We also tested whether sRNAs can travel from the central cell to the egg by expressing a microRNA in the central cell that targets cleavage of green fluorescent protein (GFP) RNA expressed from a transgene in the egg, analogous to an experiment performed earlier in pollen (7). The central cell-expressed microRNA substantially reduced GFP fluorescence in the

egg (fig. S12 and table S5), which suggests that central cell sRNAs can travel into and function in the egg.

If silencing induced by companion cell sRNAs occurs at the transcriptional level, lack of DME in the companion cell would be expected to reduce RdDM of DME target sequences in gametes. Indeed, overall CHH methylation of TEs is decreased in *dme*<sup>+</sup> sperm compared with wild-type sperm (Fig. 2E), and CG sites demethylated by DME in vegetative cells show preferential CHH hypomethylation in *dme*<sup>+</sup> sperm (Fig. 4, B and D). Conversely, loci that exhibit decreased CHH methylation in *dme*<sup>+</sup> sperm show increased CG methylation in *dme*<sup>+</sup> vegetative cells (Fig. 4, C and D). Thus, DME activity in the vegetative cell is required for full methylation of a subset of sperm TEs, which indicates that demethylation in companion cells generates a mobile signal—probably sRNA—that immunizes the gametes against TE activation. This conclusion is supported by the specific CHH hypermethylation of small, endosperm-demethylated TEs observed in the rice embryo (13).

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**Acknowledgments:** We thank S. Harmer for assistance with the analysis of histone modifications, the BioOptics team at the Vienna Biocenter Campus for sorting sperm and vegetative cell nuclei, K. Slotkin for the *LAT52p-amiRNA-GFP* plasmid, and G. Drews for the *DD45p-GFP* transgenic line. This work was partially funded by an NIH grant (GM69415) to R.L.F., NSF grants (MCB-0918821 and IOS-1025890) to R.L.F. and D.Z., a Young Investigator Grant from the Arnold and Mabel Beckman Foundation to D.Z., an Austrian Science Fund (FWF) grant P21389-B03 to H.T., a Ruth L. Kirschstein NIH Predoctoral Fellowship (GM093633) to C.A.I., a Fulbright Scholarship to J.A.R., a fellowship from the Jane Coffin Childs Memorial Fund to A.Z., and a Robert and Colleen Haas Scholarship to D.R. Sequencing data are deposited in GEO (GSE38935).

#### Supplementary Materials

[www.sciencemag.org/cgi/content/full/337/6100/1360/DC1](http://www.sciencemag.org/cgi/content/full/337/6100/1360/DC1)  
Materials and Methods  
Supplementary Text  
Figs. S1 to S12  
Tables S1 to S5  
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17 May 2012; accepted 11 July 2012  
10.1126/science.1224839

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**Gene Expression and Epigenetics (10-489):** The Section of Molecular Biology invites applications for a tenure-track faculty position in Gene Expression and Epigenetics at the Assistant Professor level. Candidates pursuing innovative research on the mechanisms of eukaryotic gene expression, particularly in the area of epigenetics and epigenomics are encouraged to apply. Potential areas of interest include but are not limited to transcription, translation, mRNA stability, mRNA splicing and processing, chromatin dynamics, histone variants and modifications, non-histone chromosomal proteins, histone exchange and turnover, nuclear organization, and RNA-based mechanisms of regulation.

**Neurobiology (10-490):** The Section of Neurobiology invites applications for a faculty position at the tenure-track Assistant, Associate, or Full Professor level. Candidates at the Assistant or Associate level are expected to have a strong research program in cellular and molecular neurosciences, and to complement existing strengths in the Section of Neurobiology. Candidates at the senior level can come from any area of neuroscience and may be considered for a joint appointment in the Department of Neurosciences at the School of Medicine.

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**Systems/Quantitative Developmental Biology (10-491):** The Section of Cell and Developmental Biology invites applications for a faculty position in Developmental Biology at the tenure-track Assistant Professor or Associate Professor level. Candidates pursuing innovative research using systems, quantitative or dynamical approaches to investigate the generation, regeneration, or maintenance of a particular cell type, tissue, or organ are encouraged to apply.

Review of applications will commence by **November 1, 2012** and will continue until all the positions are filled. Interested applicants must submit a cover letter, curriculum vitae, statement of research, statement of teaching, a statement describing their past experience and leadership in fostering equity and diversity and/or their potential to make future contributions, 3-5 publications, and contact information for 3-5 references. Applications must be submitted through the University of California San Diego's Academic Personnel RECRUIT System at <https://apol-recruit.ucsd.edu/>. Further details about the required application material can be found at: [http://biology.ucsd.edu/jobs/ladder\\_info.html](http://biology.ucsd.edu/jobs/ladder_info.html).

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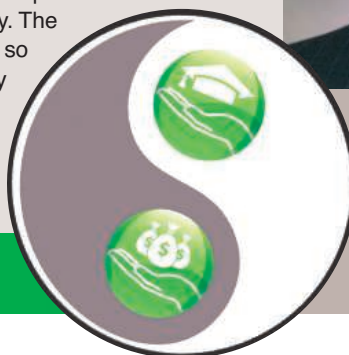


## Faculty

# Finding Balance: The Professor/Entrepreneur

The science of biology is one thing but the science of business is another animal all together. For academics who recognize that their discovery or innovation can be commercialized into a product or service for which people will actually pay, the promise of entrepreneurial endeavors can be exhilarating and confounding at the same time. Issues of intellectual property ownership, human resources protocols, and time management, as well as the challenge of keeping a delineated barrier between professorial and business activities can be difficult to manage, but these concerns shouldn't prevent academics from seeking to create a startup company. The key is to find avenues to balance the two worlds so that scientists can still continue to excel in what they do best and enjoy most—research and discovery.

By Alaina G. Levine



“Students see the passion we bring for science and entrepreneurship and it’s easier for them to see themselves doing it too.” —Gregory Phelan

## KNOW YOUR PRIORITIES

**Omid Farokhzad** has been involved with three startups and holds 60 patents, and still manages a prolific laboratory of 25 people in nanomedicine and biomaterials at Brigham and Women’s Hospital in Boston. The Harvard Medical School associate professor of anesthesiology completed his postdoc in a group headed by MIT’s Robert Langer, where “the mindset of doing translational work was part of my training,” he says. So commercializing technology while contributing to the academic enterprise was a natural part of his genesis as a scientific leader.

But not every scientist has the luxury of learning about patents and products from their postdoc principal investigator. When **Dave Berque**, a professor of computer science at DePauw University, started as an entrepreneur, “I was uncomfortable at first. I wondered if it is appropriate for an academic to have products that spin off research,” he shares. But soon he found himself at ease with the process of becoming an entrepreneur, he says, because this is similar to the “textbook publication model that has been long-accepted in academia, as a way of blending scholarly and commercial activities.”

If you are a professor who ponders whether your research can be developed into a technology that can be commercialized, your initial step should be to ponder your priorities. Do you want to stay in academia? Do you desire a career in industry? Deciding these choices early on, even before the lawyers and university representatives get involved, is crucial to forging a balance and a satisfying career.

Farokhzad says part of the reason he has been successful is because he recognized that “my primary goal is to be an academic, and I don’t have any desire to run any of these companies.”

## FIGURING OUT WHAT PATH TO TAKE

For every innovation that an academic thinks has market potential, there are seemingly endless ways of transferring that invention into a business. From weaving a multilayered licensing deal, to launching a company, to selling the technology outright, the dizzying array of entrepreneurial outlets can be unfamiliar territory for a professor whose training has been spent in the lab.

To wrangle the options and make it through the multiverse of marketing and manufacturing without sacrificing professorial duties, an academic’s initial stop should be their institution’s office of technology transfer (OTT).

The key is creating complete transparency from the start, suggests **Adam G. Marsh**, associate professor of marine biological science at the University of Delaware. Ensure the university knows what you are doing, and “make sure the university is happy with what you’re doing,” he advises. Get to know your institution’s human resources regulations and how they may impact your work in the private sector. For example, at Marsh’s institution, there are restrictions on how much time a professor can consult for an outside organization, he says. And there is also a rule that a faculty member can’t work for another company while employed at the university, a [continued](#)

## UPCOMING FEATURES

**Top Employers Survey—September 21 (online);  
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## The NIH Intramural Research Program is Recruiting Tenure-Track “Earl Stadtman Investigators”

The National Institutes of Health, the U.S. government’s premier biomedical and behavioral research enterprise, is pleased to announce its fourth annual call for “NIH Earl Stadtman Investigators.” Scientific discoveries from our intramural laboratories, with their extensive infrastructure and critical mass of expertise, have a crucial role in both maintaining America’s research excellence and advancing medical treatments and cures.

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**How to apply:** Applicants must submit a CV, a three-page research plan, a one-page description of their vision for future research and its potential impact, and contact information for three professional references through our online application system at <http://irp.nih.gov/stadtman> between August 1 and October 1, 2012. You will be asked to designate a primary and secondary scientific area of expertise to aid in assigning your application to the appropriate review committee. Requests for letters of recommendation will be sent to your references when you submit your application. Reference letters will be accepted via upload to the website until 11:59 p.m. EDT October 15, 2012. We cannot accept paper applications.

**What to expect:** Search committees of subject-matter experts will review and evaluate applicants based on the following criteria: publication record, scientific vision and potential scientific impact of current and proposed research, demonstrated independence, awards and references. The committees will identify the most highly qualified candidates to invite to the NIH for a lecture in November or December 2012, which will be open to the NIH scientific staff, and for subsequent interviews with the search committees. The search committee chairs and NIH Scientific Directors, who lead our intramural programs, will identify finalists to be recruited as Earl Stadtman Investigators. Candidates not selected as Stadtman finalists can still be considered for other open NIH research positions. The entire process from application review to job offer may take several months, depending on the volume of applications.

\*\*\*\*

We call upon individuals who will open our eyes to possibilities we haven’t yet envisioned, to complement our scientific mission and enhance our research efforts. More information about our program is at <http://irp.nih.gov>. The inspiring story of Earl and Thressa Stadtman’s research at the NIH is at <http://history.nih.gov/exhibits/stadtman>. Specific questions regarding this recruitment effort may be directed to Dr. Roland Owens, Assistant Director, NIH Office of Intramural Research, at [owensrol@mail.nih.gov](mailto:owensrol@mail.nih.gov). DHHS and NIH are Equal Opportunity Employers.

# PURDUE

## UNIVERSITY

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Campus programs of relevance to this cluster hire include the Indiana Clinical and Translational Science Institute <http://www.indianactsi.org>, Regenstrief Center for Healthcare Engineering <http://www.purdue.edu/discoverypark/rcche/>, Purdue University Center for Cancer Research <http://www.cancerresearch.purdue.edu/>, and Discovery Park <http://www.purdue.edu/discoverypark/>

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One Assistant Professor position is available. Areas of interest include, *but are not limited to*, user interface design for healthcare and/or Healthcare Informatics applications, large scale health behavior patterns data mining and scientific visualizations, user-friendly mobile computing applications for patient homecare monitoring, innovative user interfaces for making Healthcare Informatics easily accessible to non-technical populations, information sharing among healthcare providers through informal communities using virtual community and social networking technology, alternate approaches for professional communications in Healthcare Informatics, simulation and gaming.

**For information specific to each position go to: <http://www.purdue.edu/discoverypark/ClusterHireinPublicHealth>**

Successful candidates will be expected to develop an internationally-recognized research program, interact with diverse faculty, staff and students across campus, contribute to the further development of prevention of chronic disease/public health as an area of excellence on the Purdue University campus, demonstrate excellence in teaching, and function as an active member of the departmental and university faculty. Purdue University is a large and vibrant life and health science community. Our faculty spans disciplines that include basic and social sciences, agriculture, veterinary medicine, pharmacy, and engineering. Faculty members also participate in interdisciplinary programs in health and human sciences.

Applicants should have a PhD or MD, post-doctoral experience depending on field of study, a strong publication record, the potential to develop a vigorous, extramurally-funded research program, and a commitment to research and teaching excellence. Applications should include in a single pdf file a cover letter, curriculum vitae, two-page summary of research interests, and a one-page teaching statement. Applications and three letters of recommendation should be submitted electronically to [haan@purdue.edu](mailto:haan@purdue.edu). Screening of applications will begin upon receipt and will continue until the positions are filled.

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**Requirements:** Applicants should submit a single pdf-formatted file including a cover letter, curriculum vitae, a statement of accomplishments and future priorities in research and teaching, and a list of three references (with contact information). Applications should be sent to [Bioinformaticsfaculty-search@wpi.edu](mailto:Bioinformaticsfaculty-search@wpi.edu). Review of applications will be conducted on a rolling basis and continue until the position is filled.

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The Program in Bioinformatics and Integrative Biology is housed in the new state-of-the-art Albert Sherman building next to Program in Systems Biology and the RNA Therapeutics Institute. The closely collaborating Program in Gene Function and Expression, Program in Molecular Medicine, and Department of Biochemistry and Molecular Pharmacology are located in neighboring buildings. The Program is supported by high-performance computing facilities. Salary and start-up package will be highly competitive and commensurate with the high level of accomplishment expected of successful applicants.

Applicants should submit a cover letter explaining their interest in the Program, a curriculum vitae that includes publications, honors, and a succinct research plan to <http://www.academicjobsonline.org>. To expedite the review process, applicants should invite three individuals who are familiar with their work and potential for success to upload their recommendation letters at the same web address. Review of applications will begin on **November 1, 2012** and continue until positions are filled. Inquiries, but not application materials, may be directed to **Professor Zhiping Weng** at [zhiping.weng@umassmed.edu](mailto:zhiping.weng@umassmed.edu).

UMASS Medical School has built a reputation as a world-class research institution in basic and clinical research. The Medical School attracts more than \$250 million in research funding annually, 80 percent of which comes from federal funding sources. The Medical School is located within a ten-minute drive from Worcester Polytechnic Institute (WPI). The two Universities have numerous joint research and educational efforts in Bioinformatics and Systems Biology.

*As an Equal Opportunity and Affirmative Action Employer, UMMS recognizes the power of a diverse community and encourages applications from individuals with varied experiences, perspectives and backgrounds.*



University of  
Massachusetts  
Medical School



PROGRAM IN  
SYSTEMS BIOLOGY

## Faculty Positions Program in Systems Biology

The newly established Program in Systems Biology invites applications from outstanding candidates for a **tenure-track or senior tenured professor position**. Rank will be commensurate with ability and experience. The positions will be highly competitive with regard to start-up funds, laboratory space, and salary.

We are seeking innovative, energetic and collaborative individuals who will develop a strong experimental research program to tackle important problems in one of the following areas in systems biology: Network Biology, Single Cell Systems Biology, Genome Biology, Evolution and Variation, Systems Biology of Human Disease, Proteomics. Exceptionally strong candidates in other areas will also be considered.

The Program in Systems Biology is housed in the new state-of-the-art Albert Sherman Center. The Program is adjacent to the Program in Bioinformatics and Integrative Biology and the RNA Therapeutics Institute. The Program has high-performance computing facilities and a full-time systems administrator to support the research activities of its Faculty. Further information on the Program can be found at [www.umassmed.edu/psb](http://www.umassmed.edu/psb).

Applicants should submit a cover letter explaining their interest in the Program, a curriculum vitae that includes publications and a succinct research plan to <http://www.academicjobsonline.org>. To expedite the review process, applicants should invite three individuals who are familiar with their work and potential for success to upload their recommendation letters at the same web address. Review of applications will begin on **November 1, 2012** and continue until positions are filled. Inquiries, but not application materials, may be directed to **Professors A.J. Marian Walhout** ([marian.walhout@umassmed.edu](mailto:marian.walhout@umassmed.edu)) or **Job Dekker** ([job.dekker@umassmed.edu](mailto:job.dekker@umassmed.edu)).

The University of Massachusetts Medical School has built a reputation as a world-class research institution in basic and clinical research. The Medical School attracts more than \$250 million in research funding annually, 80 percent of which comes from federal funding sources. UMASS Medical School is located within a 10 minute drive from Worcester Polytechnic Institute (WPI). The two Universities have numerous joint research and educational efforts in Systems Biology and Bioinformatics.

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# Faculty



“I utilize wide disclosure to audiences during speeches.”

—Phillip Sharp

stipulation that is common throughout academia.

The OTT can assist faculty with understanding how much time they can spend on outside endeavors and how it must be structured. Technology transfer professionals also provide insight into patent law and can help professors navigate intellectual property (IP) issues. But you need to be proactive, recommends Berque, and find out your school’s IP policies early on. “The worst time to ask,” he notes, “is after you launch, when the stakes are high and you have value.”

**Gregory Phelan**, an associate professor and chair of the chemistry department at SUNY College at Cortland, jokes about intellectual property: “If you’re breathing university air, they have the right to it.” Professors need to have an IP plan from the start and should engage their university’s tech transfer office early on. The collaboration between the professor and their OTT will be a vital factor in ensuring that the proper balance and separation is maintained between their entrepreneurial and academic endeavors. But “do not labor under the misconception that your tech transfer office automatically knows what to do with your research, because they probably don’t,” cautions **Michael Zemel**, a professor of nutritional science and medicine at the University of Tennessee. “You’ll need to explain what the commercial value is, the utility of your work, and who would benefit. Insist on a conversation.”

Although there are multiple avenues to engage in entrepreneurship, many professors choose to license their technology to an existing firm or start their own company, and then back off. They might serve as a science advisor, but they prioritize their time so that they can maintain their teaching and research loads while offering outside counsel to industry. “My primary commitment is to MIT,” says Nobel Laureate **Phillip Sharp**, who cofounded Biogen in 1978 and served as chair of its science advisory board and then as a member of the board of directors for 20 years. “MIT and Biogen recognized that my interactions would be limited to one day a week.”

**Joop Gäken**, a senior lecturer in the School of Medicine at King’s College London, has three patents. When he licensed his microRNA target identification technology to a company, he did so in part to forge equilibrium between the two worlds he was straddling. “Because we

## Featured Participants

**Biogen Idec**  
www.biogenidec.com

**Brigham and Women’s Hospital**  
www.brighamandwomens.org

**DePauw University**  
www.depauw.edu

**Harvard Medical School**  
hms.harvard.edu

**King’s College London**  
www.kcl.ac.uk/medicine/index.aspx

**Marquette University**  
www.marquette.edu

**MIT**  
www.mit.edu

**Oklahoma University Health Science Center**  
ouhsc.edu

**SUNY College at Cortland**  
www2.cortland.edu/home

**The University of Tennessee**  
www.utk.edu

**University of Delaware**  
www.udel.edu

didn’t spin off our own company, it hasn’t been disruptive for me,” he explains. “Keeping the balance was not very difficult, and I still did most of the same work I was doing before.”

## MANAGING POTENTIAL CONFLICTS OF INTEREST

Once you engage in entrepreneurship, you must create a distinct separation between your university lab and your company’s facilities. IP can’t flow freely between the two, and neither can labor—your grad students cannot work for you in your group and intern at your company at the same time. Safeguards that prevent mingling are necessary for legal purposes, say experts, as well as to synthesize a balance between being in academia and being in business.

**David Baker**, a professor of biomedical sciences in the College of Health Sciences at Marquette University, partnered with his institution to set up “firewalls” to manage any potential conflict of interest that could occur. The university enlisted the help of a third party contractor, he explains, who implemented certain checkpoints that would catch and resolve possible concerns.

“There is a demarcated line between my academic labs and the companies that got started in part through my inventions,” says Farokhzad. Anything that is or could appear to be a conflict of interest is immediately shuttered. He doesn’t accept sponsored research from companies, either his own or others, and any work that is “earmarked for the companies doesn’t connect with my academic lab.” And to ensure that his postdocs and staff don’t feel they are doing work in the lab that can be funneled into one of his ventures, he encourages open discussion about patents and he generally doesn’t transfer any IP discovered in his academic lab into an old company. Instead, “if the new IP is viewed as game-changing, then it may form the foundation for a new company.”

Sharp urges that an almost excessive amount of communication about your dual paths is warranted to prevent even **continued**

CREDIT: PHOTO IS THE PROPERTY OF DR. SHARP’S OFFICE

EMBL



*The European Molecular Biology Laboratory is searching for Team and Group Leaders. EMBL offers a highly collaborative, uniquely international culture. It fosters top quality, interdisciplinary research by promoting a vibrant environment consisting of young, independent researchers with access to outstanding graduate students and postdoctoral fellows. EMBL is an inclusive, equal opportunity employer offering attractive conditions and benefits appropriate to an international research organisation.*

## Team and Group Leader Opportunities at EMBL Heidelberg, Germany

### TEAM / GROUP LEADER

#### COMPUTATIONAL BIOLOGY / BIOINFORMATICS

EMBL's headquarters in Heidelberg host four research units: Cell Biology and Biophysics, Developmental Biology, Genome Biology as well as Structural and Computational Biology. Bioinformatics activities are integral to the interdisciplinary research activities at EMBL and thus we seek to recruit an outstanding Group or Team Leader, working in the broad area of computational biology and bioinformatics, who would utilise the highly interdisciplinary and collaborative environment at EMBL Heidelberg.

Our search for candidates is deliberately broad and comprises all areas of computational biology that are complementary and synergistic to existing research activities at EMBL Heidelberg. Possible research areas comprise but are not limited to structural bioinformatics (e.g. modelling of protein complexes and their interactions and/or dynamics in a cellular context), image analysis/visualisation (e.g. reading out data from GFP screens, E-tomograms or visualising a virtual cell atlas), cheminformatics (e.g. chemical-protein-network analysis), systems bioinformatics (e.g. tissue modelling, analysis network perturbations) or transcriptional regulation/epigenetics (e.g. chromatin modification analysis).

We are open to applications from candidates who wish to focus entirely on their own research projects and, because there is an increasing need to integrate and streamline the multiple computational approaches followed within EMBL, to candidates who wish to function at the interface between research and service activities. The successful candidate should demonstrate a strong motivation to work in the multidisciplinary and collaborative environment of EMBL, reaching out to the many other computational and experimental groups.

For further information about this position please contact [recruitment@embl.org](mailto:recruitment@embl.org).

Interviews are planned for 6 and 7 December 2012.

### GROUP LEADER

#### GENOME BIOLOGY

The Genome Biology Unit studies the molecular mechanisms by which genetic information is expressed and regulated to yield complex biological systems, and how genetic variation leads to phenotypic diversity. The Unit addresses questions at different scales, ranging from detailed mechanistic studies (using genetics, chemistry, biochemistry and microfluidics) to genome-wide studies (using functional genomic, proteomic and computational approaches). This powerful combination enables the unit to dissect and model complex processes going from genotype to phenotype.

This group leader position provides a very competitive package to support an independent research group in an excellent scientific and highly collaborative environment. We particularly encourage candidates applying a systems biology approach to understanding specific aspects of gene expression regulation, evolution, metabolomics, stem cell biology or genomic applications to health to apply, but welcome candidates with demonstrated excellence in any area of genome biology.

Further information about the position can be obtained from the Joint Heads of Unit Eileen Furlong ([eileen.furlong@embl.de](mailto:eileen.furlong@embl.de)) or Lars Steinmetz ([lars.steinmetz@embl.de](mailto:lars.steinmetz@embl.de)).

Interviews are planned for 28, 29 and 30 November 2012.

#### APPLICATION INSTRUCTIONS

Please apply online through [www.embl.org/jobs](http://www.embl.org/jobs) and include a cover letter, CV and a concise description of research interests and future research plans. Please also arrange for 3 letters of recommendation to be emailed to [references@embl.de](mailto:references@embl.de) at the latest by 21 October 2012.

Further information on Team/Group Leader appointments can be found under [www.embl.org/gl\\_faq](http://www.embl.org/gl_faq).

For more information please visit:

[www.embl.org](http://www.embl.org)



## Program Leader in Bioinformatics

### **BACKGROUND**

We are seeking an innovative investigator with a strong research background in Bioinformatics and Computational Biology to lead an independent research program within the Victor Chang Cardiac Research Institute (VCCRI), Sydney, Australia. The VCCRI is an independent research organization committed to excellence in both basic and translational biomedical research. The VCCRI is affiliated with the University of New South Wales (UNSW), and a member of the St. Vincent's Research Precinct that also involves the Garvan Institute for Medical Research and the St. Vincent's Centre for Applied Medical Research.

Preference will be given to individuals applying next generation sequencing or other high throughput technologies and bioinformatics and computational tools to identify alleles, genes and pathways contributing to common disease.

The successful candidate will be provided with office and support space, and significant financial support to rapidly establish their program, and will be eligible for an academic appointment at UNSW.

### **RESPONSIBILITIES**

Your research program might focus on one or more of the following areas, closely linked with experimental science within the VCCRI: mutation detection, transcriptional regulation, epigenetics, transcriptomics, non-coding RNAs, imprinting, disease susceptibility, structural variation, evolution. The successful applicant will be expected to lead a vigorous independent research program, maintain extramural research funding, and participate in graduate and postdoctoral training.

### **REQUIREMENTS**

PhD/DPhil/MD in the fields of computational biology, genetics or genomics. Candidates will have expertise that includes high throughput data generation and analysis, excellent verbal and written communication skills, relevant research and teaching experience, a record of high quality peer-reviewed publications, and a strong interest in innovative and interactive research.

### **ENQUIRIES**

If you have any questions about this position please reach out to Sheryl Maharaj in the first instance via email: [Sheryl.Maharaj@victorchang.edu.au](mailto:Sheryl.Maharaj@victorchang.edu.au).

### **HOW TO APPLY**

Interested candidates should submit their curriculum vitae, statement of research interest and names of three references to [Sheryl.Maharaj@victorchang.edu.au](mailto:Sheryl.Maharaj@victorchang.edu.au).

### **CLOSING DATE**

Applications will be accepted until 31 October 2012.

### **POLICY**

The VCCRI is an Equal Opportunity/Affirmative Action employer and boasts a record of gender parity at all levels of the organization.



### Assistant/Associate Professor Appointment

Applications are invited for a full-time, tenure track Assistant/Associate Professor in the Faculty of Pharmaceutical Sciences, The University of British Columbia. The Faculty has identified several research priorities, including chronic disease management and personalized medicine. Applicants should possess a Ph.D., Pharm D./Ph.D. or M.D/Ph.D in a life science or health science discipline, and have at least two years of postdoctoral research experience. The successful candidate will be expected to develop and maintain an active extramurally-funded, internationally recognized research program and participate in the training and supervision of graduate students and postdoctoral research fellows. Additionally, the successful candidate will be responsible for the coordination and teaching of pathophysiology content of the B.Sc. (Pharm.) curriculum and related teaching areas as necessary. Excellent teaching and communication skills, as well as a strong commitment to undergraduate, graduate and post-doctoral education are essential.

The Faculty of Pharmaceutical Sciences is entering a stage of unprecedented growth and expansion, and is now located in a new state-of-the-art, \$155 million facility with world-class infrastructure and equipment on the UBC Vancouver campus. The building will also house one of the Faculty's key partners, the Centre for Drug Research and Development ([www.cdrrd.ca](http://www.cdrrd.ca)), and is within easy reach of other major health science faculties and core research facilities.

Salary is negotiable, commensurate with experience, and is subject to final budgetary approval. The closing date for applications is **October 31, 2012**. Preferred start date is July 1, 2013. Interested individuals are requested to submit a letter of application with a brief description of research interests, a curriculum vitae, copies of up to five publications, a statement of teaching philosophy, and the names of four referees to:

**Chair, Pathophysiology Search Committee**  
**Faculty of Pharmaceutical Sciences, The University of British Columbia**  
**Please submit electronic applications to the Chair at: [pharmacy.newrecruit@ubc.ca](mailto:pharmacy.newrecruit@ubc.ca)**  
**Faculty Website: <http://www.pharmacy.ubc.ca/>**

### Professorship in Adherence

Applicants are invited to apply for a new full-time tenure-track faculty position in Adherence in the Faculty of Pharmaceutical Sciences at The University of British Columbia. This Professorship is being initiated in the Faculty with the objective of providing a neutral, balanced voice and an opportunity for ongoing dialogue and research on the extent of the problem and to establish efforts toward improving adherence. Candidates will hold a doctorate in pharmacoeconomics, health services research, pharmacy practice, or related discipline, and preferably with post-doctoral and previous research experience. The successful candidate will be appointed to the rank appropriate to their level of experience.

The successful applicant will develop a strong, innovative, multi-disciplinary program of research in adherence, with a focus on the role of pharmacy and collaboration with other health care disciplines. An ability to build partnerships with a wide variety of stakeholders and to provide national and international leadership in the field is essential. The candidate should have demonstrated expertise in a field germane to the study of adherence, strong leadership skills, and an ability to integrate easily into a multi-disciplinary research environment. Applicants must have demonstrated competence in teaching both at the undergraduate and graduate level. The candidate should also have demonstrated ability in establishing an active, extramurally funded research program.

The successful candidate will focus on developing methodologies that will have the greatest impact to assist pharmacists with developing adherence plans for complex regimens to optimize patient health outcomes. The primary functions of the successful candidate will include: educating students and health practitioners with an increased emphasis on the clinical skills required to support medication adherence, especially among patients with chronic diseases; evaluating different sets of adherence tools to look for synergies, efficiencies and optimal solutions for patient care; developing strong inter-professional teams to create and implement successful models of adherence; re-aligning business practices to enable personal counselling and individualized solutions in community pharmacy environments; and identifying workable and practical adherence approaches and methodologies that will influence drug plan benefits and policy to ensure optimal care for patients.

### Professorship in Sustainable Health Care

The Faculty of Pharmaceutical Sciences at The University of British Columbia invites applications for a new full-time tenure-track faculty position to lead the Initiative for Sustainable Health Care in BC. Applicants are invited to apply if they hold a doctorate in pharmaceutical policy research, health economics, pharmacoeconomics, health services research, epidemiology, or related discipline, preferably with post-doctoral and previous research experience. The successful candidate will be appointed to the rank appropriate to their level of experience.

The Initiative in Sustainable Health Care is being initiated in the Faculty of Pharmaceutical Sciences, University of British Columbia, with the objective of providing a neutral, balanced voice and an opportunity for ongoing dialogue and research on economic principles of health care sustainability, with a focus on the role of pharmacy and pharmaceuticals in effecting change.

The successful applicant will develop a strong, innovative, multi-disciplinary program of research in Sustainable Health Care, with a focus on the role of pharmacy and pharmaceuticals. An ability to build partnerships with a wide variety of stakeholders and to provide national and international leadership in the field is essential. The candidate should have demonstrated expertise in both public and private health care insurance, strong leadership skills, and an ability to integrate easily into a multi-disciplinary research environment. Applicants must have demonstrated competence in teaching both at the undergraduate and graduate level. The candidate should also have demonstrated ability in establishing an active, extramurally funded research program.

Salary is negotiable, commensurate with experience, and is subject to final budgetary approval. The closing date for applications is **November 15, 2012**. Preferred start date is May 1, 2013. Interested individuals are requested to submit a letter of application, with a brief description of research interests, a curriculum vitae, copies of up to five publications, a statement of teaching philosophy, and the names of four referees to:

**Dr. Peter J. Zed, Associate Dean, Practice Innovation**  
**Faculty of Pharmaceutical Sciences, The University of British Columbia**  
**Please submit electronic applications to: [pharmacy.practiceinnovation@ubc.ca](mailto:pharmacy.practiceinnovation@ubc.ca)**

*UBC hires on the basis of merit and is committed to employment equity. All qualified persons are encouraged to apply. We especially welcome applications from visible minority groups, women, Aboriginal persons, persons with disabilities, persons of minority sexual orientations and gender identities, and others with the skills and knowledge to engage productively with diverse communities. Canadians and permanent residents of Canada will be given priority.*

## Faculty

the perception of misconduct. “I utilize wide disclosure to audiences during speeches,” he says.

University of Delaware’s Marsh even keeps separate computer systems for his university and company research.

### FINDING THE RIGHT PEOPLE

“I’m very comfortable working with the investors that I trust and leave it to their judgment to bring in the best business and scientific team to advance our technologies,” says Farokhzad, pointing to a lesson that many faculty learn early on even in academia—surround yourself with talented people and you will shine.

“Your company will be more successful if you personally don’t do stuff that you are not good at,” says Marsh. “One has to recognize the difference between what you ‘can do’ because of related prior experience and what you ‘should not be doing’ because of overconfident ignorance.” For example, he adds, negotiating a license agreement with your institute’s OTT should be handled by a lawyer familiar with the commercial value of similar IP.

Marsh launched his company in 2009 and serves as its chief scientific officer. On paper he is not employed by the firm, but rather serves as a consultant. His advice is echoed by other successful professor-entrepreneurs: “Find the best business partners you can,” especially people with experience managing startups.

A synergistic team will help you productively manage your time. “Get ready for a busy life: one that is three times as busy,” jests Phelan. “I was surprised how busy I was. I couldn’t believe it took this much time to get a company started, funded, and a product made.”

### GETTING ROI ON THE FACULTY SIDE

“As daunting as it seems, entrepreneurship is very worthwhile,” says Baker. “It has energized me and even though I have fewer publications than I would otherwise have, I’m so much more enthused about my research.” Moreover, his interaction with patients who have benefited from his technology “gives us a real sense that what we’re doing may have a profound impact in addressing unmet medical needs. We wouldn’t have this without the entrepreneurship.”

Even with a targeted separation of academic and business endeavors, pursuing commercialization can actually enhance your skills in education. “My computer science classes are better because I can bring in my own experiences from my work,” says Berque. “This influences students to think about innovation and entrepreneurship as career paths.” He draws on examples from his software company, and ultimately, he says, “I serve as a more informed career counselor.” His professional advice is augmented with contacts in the business world who can arrange for pupils to



“My computer science classes are better because I can bring in my own experiences from my work.”

—Dave Berque

acquire internships and jobs, or to pursue other kinds of research collaborations.

“Students see the passion we bring for science and entrepreneurship and it’s easier for them to see themselves doing it too,” echoes Phelan.

The connections that faculty make not only help the students but benefit the department and university as a whole as well. Phelan describes how after speaking with local businesses about his technology, he invited an industry representative to serve on a department board, which helped bolster the department’s profile for fundraising and public relations purposes, and generally paved the way for more interactions between university and industrial scientists.

**Paul DeAngelis**, a professor of biochemistry and molecular biology at Oklahoma University Health Science Center, notes that being an entrepreneur opens up the academic to novel potential revenue streams, even with a hard separation between the activities. “NIH isn’t the golden ticket that is going to be feeding you forever,” he cautions. “My advice is to not rely solely on NIH resources if you have the ability to create a company and a drug or device that can help people.”

Entrepreneurship activity invariably also helps scientists improve their ability to articulate concepts to numerous publics. “As you explain complicated scientific processes to different audiences,” says Phelan, “it makes you a better teacher and helps improve your critical thinking and communications skills.” In addition, as you gain more knowledge about the commercialization process, and have a better understanding of the business world, you can improve your grant proposals. “Your work is directly benefiting society and humankind,” he continues. “Entrepreneurship helps make grant applications stronger, because it stimulates new ideas and demonstrates potential commercial partners,” giving you more return on your investment. If you can establish in your proposal that your innovation has commercial appeal, adds DeAngelis, it further increases your chances of landing the grant.

An entrepreneurial undertaking has myriad benefits on the academic side, and in the long run can help you reset your priorities as a scientist. Farokhzad emphasizes that entrepreneurship has helped him be a better professor because it has sharpened his ability in identifying significant research problems. “It takes just as much time and capital to work on really important problems as it does on the less important ones,” he says. “As an academic entrepreneur, you’re required to have that litmus test—is this impactful research? If not you let it go.”

*Alaina G. Levine is a science writer based in Tucson, AZ.*

DOI: 10.1126/science.opms.r1200122





**PRINCETON  
UNIVERSITY**

**ASSISTANT PROFESSORSHIP  
ANIMAL BEHAVIOR**

Princeton University's Department of Ecology and Evolutionary Biology plans to hire a tenure track assistant professor focusing on quantitative animal behavior. The Department has broad interests in behavior ecology, behavioral dynamics, behavioral endocrinology and behavioral links to other features of organismal biology. We seek applicants who pursue research that aims for significant conceptual and/or empirical integration across traditional areas of animal behavior and who have a strong commitment to teaching. It is possible that an appointment may be joint with Princeton's Environmental Institute, especially if the applicant's research focuses on problems of global or environmental change.

Applicants should write a vision statement, no longer than 2 pages, that outlines the conceptual dimensions of one or more major unsolved problems in their field and how their approach will contribute to solving them. The vision statement should be more than a summary of the applicant's prior and current research. Applications, including the vision statement, curriculum vitae, three reprints and three letters of recommendation, can be submitted online via <http://jobs.princeton.edu>, requisition #1200573. Screening of applications begins **15 October 2012**.

*Princeton University is an Equal Opportunity Employer and complies with applicable EEO and Affirmative Action regulations.*



**TENURE-TRACK  
ASSISTANT  
PROFESSORSHIPS IN  
CHEMISTRY**  
Harvard University  
Faculty of Arts and  
Sciences

**Department of Chemistry and  
Chemical Biology  
Cambridge, MA**

Candidates are invited to apply for a tenure-track assistant professorship in inorganic chemistry (<https://academicpositions.harvard.edu/postings/4246>), broadly defined to include reaction chemistry, with potential connections to energy-related research; and, physical chemistry (<https://academicpositions.harvard.edu/postings/4247>). These appointments are expected to begin on July 1, 2013. The tenure-track professors will be responsible for teaching at the undergraduate and graduate levels. We are seeking candidates who have an outstanding research record and a strong commitment to undergraduate and graduate teaching. Ph.D. required by expected start date. Candidates should arrange to have three letters of recommendation sent independently and provide a curriculum vitae, statement of teaching philosophy, list of publications, and outline of their future research plans. All applications and supporting materials must be submitted via the ARIES portal (see links above) no later than **October 15, 2012**.

*Harvard is an Equal Opportunity/Affirmative Action Employer. Applications from women and minorities are strongly encouraged.*



**UCL**

UCL Faculty of Life Sciences

**Director of Sainsbury Wellcome Centre for  
Neural Circuits and Behaviour**

University College London (UCL), the Gatsby Charitable Foundation, and the Wellcome Trust invite applications for the post of Director of a major new neuroscience centre to be based at UCL: the Sainsbury Wellcome Centre for Neural Circuits and Behaviour. This Centre will address a fundamental challenge in modern biology, determining how neural circuits process information and direct behaviour. Advances in this field will transform understanding of brain function, and ultimately lead to new ways of monitoring and regulating brain activity in health and disease.

The Sainsbury Wellcome Centre will be housed in a new state-of-the-art building embedded at the heart of UCL. It will develop and exploit new approaches for determining anatomical and functional connectivity in neural circuits and for recording, imaging and manipulating activity in genetically defined ensembles of neurons. This experimental work will be tightly integrated with the theoretical and computational neuroscience carried out by the Gatsby Computational Neuroscience Unit which will relocate to the new building in 2014.

The new Centre will comprise 12 research groups (including the Director's) and will conduct a vibrant interdisciplinary research effort, investigating information processing in neural circuits across a range of model systems and behaviours. UCL provides the ideal environment for a new Centre undertaking such a major interdisciplinary effort in neuroscience. The Centre will draw on and catalyse the rich, wide-ranging neuroscience community at UCL, currently ranked 2nd in the world for ISI citations in neuroscience and behaviour. It will also benefit from important strengths in allied fields such as physics, chemistry, engineering, nanotechnology and biomedicine.

The post of Director carries with it a professorial title and the post holder will play a significant role in the strategic development of Neuroscience at UCL. The Director will be responsible for recruiting and nurturing outstanding research groups; and for promoting links between the Centre, UCL, and the wider scientific community. Substantial and long-term resources will be available to support the scientific work of the Director and other researchers in the Centre.

The Director of the Centre will be a visionary leader with an outstanding track record in neuroscience research related to the core mission of the Centre and with substantial experience of scientific strategy and management.

The appointment will be full time and the salary is negotiable on the professorial scale, but not less than £62,110 per annum, inclusive of London Allowance. A relocation package will be available in addition. The appointment is available from Summer 2013.

For further details about the vacancy and how to apply online please go to <http://www.ucl.ac.uk/hr/jobs/> and search on Reference Number 1275837.

If you have any queries regarding the application process, please contact Nick McGhee on [n.mcghee@ucl.ac.uk](mailto:n.mcghee@ucl.ac.uk), tel +44 (0)20 7679 8878. If you wish to discuss the post informally, please contact Professor Sir John Tooke on [j.tooke@ucl.ac.uk](mailto:j.tooke@ucl.ac.uk), tel +44 (0)20 7679 0878.

Closing Date: Monday 15th October 2012.

We particularly welcome female applicants and those from an ethnic minority, as they are under-represented within UCL at this level.

Supported by  
**wellcome**trust





## FACULTY POSITIONS AT ALL LEVELS SANFORD CHILDREN'S HEALTH RESEARCH CENTER SANFORD RESEARCH/USD

The Sanford Children's Health Research Center (CHRC, Sioux Falls, SD <http://www.sanfordresearch.org/researchcenters/childrenshealth/>), invites applications from researchers for full time faculty positions at the rank of Associate Scientist, Scientist, and Senior Scientist within Sanford Research/USD (<http://www.sanfordresearch.org/>) with commensurate rank of Assistant Professor, Associate Professor, and Full Professor in the Department of Pediatrics of the Sanford School of Medicine at The University of South Dakota. An historic \$400 million gift by philanthropist Denny Sanford has allowed for expansion of Sanford Research/USD and development of the CHRC, a center specifically focusing on children's health research. The CHRC is a two-site program with locations at Sanford Research/USD in Sioux Falls, SD and the Sanford-Burnham Medical Research Institute in La Jolla, CA.

We seek outstanding scientists with research programs that contribute to the molecular understanding and treatment of congenital defects, developmental disorders, and pediatric diseases. Applicants should hold a PhD, MD or MD/PhD degree and complement the existing strengths and the interdisciplinary and collaborative nature of the CHRC. Junior candidates will be expected to develop independent research programs with extramural funding. Senior candidates should have a demonstrated track record of extramural grant support and publications and be capable of providing mentorship to junior faculty members within the CHRC while advancing their independent research programs. Researchers will join the energetic and collegial research community at Sanford Research/USD and hold both Sanford Research/USD and Sanford School of Medicine faculty appointments.

Significant institutional support, including modern laboratory space and state-of-the-art facilities, will be provided in the Sanford Center. In addition, a comprehensive compensation package will be tailored to the individual's qualifications. Sanford Health is an Equal Opportunity/Affirmative Action Employer. Candidates should submit a single PDF including a detailed *curriculum vitae* and a description of research experience and future plans that includes relevance to children's research. Candidates should also submit at least three letters of recommendation. All application materials should be sent by email to: **David A Pearce Ph.D., Director, Children's Health Research Center, Sanford Research/USD, Professor, Department of Pediatrics, Sanford School of Medicine of The University of South Dakota, 2301 E. 60<sup>th</sup> Street North, Sioux Falls, SD 57104; Telephone: 605-312-6004 FAX: 605-312-6071; Email: [David.Pearce@sanfordhealth.org](mailto:David.Pearce@sanfordhealth.org).**



OREGON  
HEALTH & SCIENCE  
UNIVERSITY

## Assistant Professor Structural Biology

The Department of Biochemistry and Molecular Biology seeks candidates for a tenure track faculty position. Targeted areas are Membrane Proteins, the Cytoskeleton, or other Macromolecular Assemblies. Applicants are sought who could take advantage of state-of-the-art Cryo-Electron Microscopy resources at the new OHSU/FEI Living Lab (<http://tinyurl.com/cl2va5w>)

Candidates should have post-doctoral experience and be ready to direct an independent, extramurally funded research program. The recruit will contribute to training programs in Cellular and Molecular Biosciences and Quantitative Biology, as well as participate in Medical Education.

Apply online at [www.ohsujobs.com](http://www.ohsujobs.com), id IRC37050 submitting curriculum vitae, statement of research accomplishments and future research goals and three names for letters of reference prior to a deadline of **December 1, 2012**.

*OHSU is an Equal Opportunity Affirmative Action Institution.*



Massachusetts  
Institute of  
Technology

Come work with us!

## Neuroscientist

The Picower Institute for Learning and Memory at the Massachusetts Institute of Technology is seeking outstanding neuroscientists for tenure track positions at the level of Assistant Professor.

We are interested in candidates studying development and/or plasticity of brain circuits at the cellular, circuit, and/or systems levels using a multi-faceted approach combining different methodologies and levels of analysis. We are particularly seeking, though not exclusively, candidates with strong cellular/molecular training.

Academic appointments will be in the Department of Brain and Cognitive Sciences. Candidates must have a commitment to excellence in undergraduate and graduate education, and must demonstrate the ability to develop a significant and independent research program.

**Applicants should submit a curriculum vitae, a summary of current and proposed research programs, an education plan, and arrange for three letters of recommendation. Applications are being accepted at Academic Jobs Online (<https://academicjobsonline.org/ajol>).**

**Search Contact: Prof. Elly Nedivi**

**Consideration of completed applications will begin immediately. Applications will be accepted for review until December 10, 2012.**

*MIT is an affirmative action employer, and we encourage applications from women and underrepresented minorities.*



THE PICOWER  
INSTITUTE  
FOR LEARNING AND MEMORY

<http://web.mit.edu>



## Assistant Professor Positions available at Princeton University

The Lewis-Sigler Institute for Integrative Genomics at Princeton University invites applications for a tenure-track faculty position at the Assistant Professor level; faculty positions at the Lewis-Sigler Institute are joint appointments with an appropriate home department. We are seeking outstanding scientists with strong interest and experience in quantitative, systems-level approaches to understanding any area in modern experimental biology. Candidates with expertise in experimental methods for high-throughput biology are particularly encouraged to apply. A strong record of experimental work and quantitative analysis is essential. The successful candidate will have research laboratories at the Institute, and teaching responsibilities (both graduate and undergraduate) will be shared between the Institute and the home department.

The Lewis-Sigler Institute for Integrative Genomics, housed in the Carl Icahn Laboratory at Princeton University, was established to innovate in research and teaching at the interface of modern biology and the more quantitative sciences. The Institute has invested heavily in providing state-of-the-art infrastructure, including facilities for High Throughput Sequencing and Microarrays, Advanced Imaging, Mass Spectrometry, and Computation.

**Essential Qualifications:** All applicants must have a Ph.D., M.D., or equivalent degree. In addition, applicants must have a very strong record of research productivity, demonstrate the ability to develop a rigorous research program, and be committed to teaching at both the undergraduate and graduate levels.

**How to Apply:** Applications must be submitted online at: <http://jobs.princeton.edu/applicants/Central?quickFind=62744> and should include a cover letter, curriculum vitae, a two-page research description, as well as contact information for three references. Applications will be reviewed beginning on **October 15, 2012**, and applications arriving after November 15, 2012 may not be considered.

*Princeton University is an Equal Opportunity Employer and complies with applicable EEO and Affirmative Action regulations.*

The Friedrich Miescher Institute for Biomedical Research (FMI) invites applications for a tenure-track group leader position. We are seeking an outstanding individual who will establish a research program that explores the molecular mechanisms of cell fate determination in development and/or disease.

**FMI**

Friedrich Miescher Institute  
for Biomedical Research

## Group Leader Position, tenure track Cell fate determination and plasticity

Opportunities exist for collaborative interactions with other FMI research teams in **epigenetics, neurobiology and mechanisms of cancer**. The FMI provides outstanding core facilities for experimental mouse genetics, live microscopy, cell sorting, genomics, computational biology, protein crystallography and proteomics. Highly competitive salary and running budget are provided.

The FMI is an international biomedical research center with 300 members, including about 180 postdoctoral fellows and graduate students. It is affiliated with the University of Basel and is funded by the Novartis Research Foundation. The Institute runs a successful international PhD program (for further information see [www.fmi.ch](http://www.fmi.ch)). Situated in Basel, Switzerland, the FMI offers an outstanding English-speaking scientific environment in the center of Europe.

Applications, including a CV, the names and emails of three referees, and a concise description of research interests and future plans should be submitted online at:

[www.fmi.ch/gl\\_search](http://www.fmi.ch/gl_search)

Informal inquiries can be sent to:  
Dr. Susan Gasser ([susan.gasser@fmi.ch](mailto:susan.gasser@fmi.ch))  
4058 Basel, Switzerland

The closing date for applications is  
**November 30, 2012.**

### Director, Berkeley Energy & Climate Institute (BECI) University of California, Berkeley

The University of California, Berkeley is poised to take its leadership role addressing energy and climate challenges to a new level, to *catalyze a sustainable future through innovation and education for responsible stewardship of the planet* through the Berkeley Energy & Climate Institute (BECI).

We are seeking a Director of international research reputation and stature to lead the Institute to:

- Strengthen the coordination and synergies of our energy and climate efforts to achieve maximum impacts through the integration of science, engineering, social science, market, health and policy research;
- Educate and energize the next generation of energy and climate research scientists and policy/government leaders;
- Pioneer a commitment to technology transfer that sets a new global standard and leverages the rich potential for partnerships, in the Bay Area and across the globe;
- Engage the talents and creativity of our extraordinary students, alumni, community, industry and government stakeholders, and partners at Lawrence Berkeley National Lab.

Additionally, the Director will play a major role in representing UC Berkeley's vision and impacts to, and expanding support from, its outside constituencies, including without limitation: the California Legislature and its delegation in the nation's Capitol; federal and state agencies, the tax payers of California, and BECI's philanthropic and industrial sponsors.

BECI's Director will report to UC Berkeley's Chancellor. A competitive candidate must have a PhD or equivalent and possess experience at the level of tenured professor or equivalent at a research university or laboratory with national/international prominence and in an academic discipline relevant to the research agenda of BECI. S/he should have demonstrated academic and research management experience, as the equivalent of a university department chair, or as a laboratory director appointment at an industrial laboratory or government agency. Preferably, the Director will also have government and/or industry experience. The Director must be able to demonstrate considerable management experience suitable for a diverse and complex research environment that involves academia as well as private industry. An ability to interact effectively, build partnerships, and develop shared goals and objectives with a large, independent, and diverse community of researchers across multiple campuses and with industrial and government partners, is essential. An interest in subjects that will contribute to the understanding of diversity and equal opportunity is desired.

Applicants should submit a CV and statement summarizing their research interests as well as experience and professional contributions to the area of energy and/or climate research. Applications must be submitted online by **December 3, 2012** at <https://aprecruit.berkeley.edu/apply/JPF00062>.

*The University acknowledges the need to remove barriers to the recruitment, retention, and advancement of faculty from historically excluded populations who are currently underrepresented. Qualified women and members of under-represented minority groups are strongly encouraged to apply. The University of California is an Equal Opportunity Employer and is committed to addressing the needs of dual career couples.*







## Junior Faculty Positions, Vollum Institute Oregon Health & Science University, Portland OR

The Vollum Institute ([www.ohsu.edu/vollum](http://www.ohsu.edu/vollum)) solicits applications from exceptional, creative and interactive scientists for junior faculty positions, and also invites applications from candidates at an early stage in their career.

We encourage applications from candidates whose research may include, but is not limited to, *cell biology, molecular biophysics and structural biology, genetic, molecular and cellular neuroscience and neural circuitry*, and whose work will augment the emphasis on neuroscience at the Vollum Institute.

The Vollum Institute offers competitive salary, benefits and start-up funds, renovated laboratory space, ample access to numerous state-of-the-art core facilities that include cutting-edge light and electron microscopes, and extensive opportunities for collaboration both within the Institute and throughout the University.

Vollum appointments are tenure-track equivalent, full-time research positions with minimal teaching requirements. The Vollum is allied with the Neuroscience Graduate Program, providing opportunities for teaching and access to a pool of exceptional students.

OHSU is an equal opportunity/affirmative action employer committed to maintaining diversity in its faculty. Candidates can apply by sending an electronic copy of their curriculum vitae, a description of research plans and goals, and three reference letters to the Vollum Faculty Search Committee ([volljob@ohsu.edu](mailto:volljob@ohsu.edu)) by **December 1, 2012**.



## BROOKLYN COLLEGE IS NY

### Brooklyn College of The City University of New York

The Department of Biology at Brooklyn College seeks a new faculty member to begin fall 2013 to add research and teaching expertise to our growing group specializing in molecular and cell biology, including microbiology. The selected candidate will develop an independent research program to serve our highly diverse student body, will teach at the undergraduate, MA, and PHD levels. The graduate program will include teaching in a new MS and Professional Masters in Science programs that will train students for employment in academic, biomedical, and industrial settings. Any area of molecular biology research will be considered, including prokaryote and eukaryote microbiology and especially those incorporating genomics and bioinformatics. All appointments are subject to financial availability.

PhD in Biology or related field; At least two years of post-doctoral research experience or equivalent; Peer reviewed publications in molecular biology, microbiology, cell biology, or bioinformatics and interest and experience in teaching highly diverse students.

Open until filled with the review of applications to begin on November 15, 2012.

For complete job description and application instructions please see [www.brooklyn.cuny.edu/faculty2013](http://www.brooklyn.cuny.edu/faculty2013)

**No email or hard copy applications will be accepted.**

Brooklyn College is an AA/EQ/IRCA/ADA employer.



**Duke University  
School of Medicine**

### Tenure-track Faculty Position (Assistant/Associate/Full Professor) Department of Molecular Genetics and Microbiology, Duke University Medical Center

Applications are invited for a tenure-track position in the Department of Molecular Genetics and Microbiology at Duke University Medical Center (<http://mgm.duke.edu/>). We are seeking individuals that employ genetics to investigate important biological problems. There are no restrictions concerning the research area or the model organism used. Nonetheless, individuals working in the following areas are particularly encouraged to apply: (1) the genetic basis for behavior and disease in *Drosophila*, *Caenorhabditis* or mammalian models, (2) functional studies of non-coding RNAs, and (3) genetic analysis of genome stability in multi-cellular organisms.

The individual hired is expected to develop a strong, independent research program that will complement existing areas of expertise within the Department. Research strengths within the Department include RNA biology, DNA repair and recombination, microbial pathogenesis (viral, bacterial and fungal), and human/mammalian genetics.

Applications should include a *curriculum vitae*, a description of research accomplishments and plans for future research (please limit to three pages), and reprints of three representative publications. Interested applicants should submit application materials (cover letter, CV, statement of research accomplishments/interests and at least three references) for this job posting on AcademicJobsOnline at <https://academicjobsonline.org/ajo/jobs/1676>. Applications should be received by **November 15, 2012**. Further inquiries may be directed to **Rachel Mullis** at [rachel.mullis@duke.edu](mailto:rachel.mullis@duke.edu).

**The deadline for receipt of applications is November 15, 2012.**

*Women and minorities are encouraged to apply. Duke University is An Equal Opportunity/Affirmative Action Employer.*



**Duke University  
School of Medicine**

### Tenure-track Faculty Position (Assistant or Associate Professor) in the field of Human Virology Duke University Medical Center

Applications are invited for a tenure-track position at Duke University Medical Center. The position represents a partnership of the Center for Virology, Center for AIDS Research and the Departments of Medicine and Molecular Genetics and Microbiology. We are seeking individuals studying pathogenic human viruses, in particular the genetics and molecular biology underlying differences in virus replication and pathogenesis. Scientists studying viruses that cause, or have the potential to cause, a significant human disease burden are especially encouraged to apply. This individual is expected to develop an independent research program related to a topic of interest, while also synergizing with existing strengths and research programs within the center and the departments.

Applications should include a *curriculum vitae*, a description of research accomplishment and plans for future research, and reprints of three representative publications. Applicants should also arrange to have three letters of recommendation submitted on their behalf. Application materials should be uploaded at: <https://academicjobsonline.org/ajo/jobs/1677>. Further inquiries may be directed to **Rachel Mullis** at [rachel.mullis@duke.edu](mailto:rachel.mullis@duke.edu).

**The deadline for receipt of applications is November 15, 2012.**

*Women and minorities are encouraged to apply. Duke University is An Equal Opportunity/Affirmative Action Employer.*

## Faculty Positions in Gene Regulation and Genomics

The Cecil H. and Ida Green Center for Reproductive Biology Sciences and the Division of Basic Reproductive Biology Research in the Department of Obstetrics and Gynecology at the University of Texas Southwestern Medical Center in Dallas invite applications from outstanding candidates for three tenure-track assistant professor positions in signaling, gene regulation, and genome function, especially in the areas of chromatin and transcription, epigenetics, nuclear endpoints of cellular signaling pathways, nuclear receptors, RNA biology, genome organization and evolution, and DNA replication and repair. We are interested in a wide variety of model systems and experimental approaches, including biochemistry, molecular biology, structural biology, animal models, genomics, proteomics, bioinformatics, and computational biology. The Green Center's research programs focus on, but are not limited to, reproduction and development in a broad sense, including: oocyte maturation, fertilization, development, pregnancy, parturition, stem cells, endocrinology, and oncology, as well as relevant aspects of metabolism, inflammation, immunity, and neurobiology.

• **Position 1: Signaling, chromatin, and gene regulation** – a broad search for candidates using a wide array of experimental approaches to address fundamental questions in nuclear signaling, chromatin, transcription, epigenetics, and RNA biology.

• **Position 2: Genomic, bioinformatic, computational, and evolutionary approaches to understanding gene regulation** - a more focused search in areas that will connect to broader genomic initiatives on campus.

• **Position 3: Molecular biology of female reproductive systems** - a search for candidates using cell-based or physiological models in combination with molecular or genomic approaches to address fundamental questions concerning female reproductive biology.

The Green Center is an endowed basic science research center at UT Southwestern, which promotes and supports cutting-edge, integrative, and collaborative basic research in female reproduction and related areas of biology, as well as strong connections between basic and clinical research. This recruitment is part of a major university- and department-supported renovation and rejuvenation of the Green Center (upwards of 12 million dollars when completed and fully staffed). Successful candidates, who will be housed in a newly renovated state-of-the-art research facility and provided a generous start-up package, are expected to establish scientifically rigorous and externally funded research programs and participate in center, department, and university teaching and training programs. To learn more about the Green Center, visit: <http://www.utsouthwestern.edu/utsw/home/research/greencenter/>.

Candidates must have a Ph.D. or M.D. or equivalent in a relevant field of study, postdoctoral or comparable experience, and a demonstrated record of research excellence. Applicants should send a letter of application, curriculum vitae, and a statement of planned research projects as pdf files to **GreenCenter@UTSouthwestern.edu**, indicating the position of interest (1, 2, or 3) in the subject line. Applicants should also arrange for three letters of reference to be sent directly to the above e-mail address. Review of applications will begin on **October 31, 2012** and continue during the 2012 – 2013 academic year or until the positions are filled, although applicants are encouraged to submit their materials as soon as possible.

*UT Southwestern is an Equal Opportunity/Affirmative Action Employer.*



## College of Liberal Arts and Sciences School of Molecular and Cellular Biology Departments of Molecular and Integrative Physiology and Cell and Developmental Biology Assistant Professors

The School of Molecular and Cellular Biology (<http://mcb.illinois.edu/>) at the University of Illinois at Urbana-Champaign seeks outstanding applicants for two tenure track Assistant Professor positions in the following areas:

**Cellular Growth Mechanisms and Cancer:** Areas of interest include (i) signaling networks and stem cells in cell growth and cancer, (ii) development of animal models, tumor biomarkers and small molecules for treatment of cancer, (iii) proteomic and genomic approaches to analysis of tumor biology and early detection of tumors (iv) epigenetic basis of cancer, (v) hormone-dependent cancers, (vi) stromal-cancer cell interactions, (vii) immunological approaches to cancer therapy; (viii) novel systems and synthetic biology approaches to cell growth regulation and cancer.

**Regenerative Biology and Reproduction:** Areas of interest include (i) genomic approaches and animal models to study developmental aspects of reproduction and embryogenesis, (ii) signaling mechanisms regulating maternal-fetal dialogue during implantation and placentation, (iii) epigenetic basis of fetal abnormality and childhood diseases, (iv) basic mechanisms for tissue and organ regeneration and stem cell biology.

Candidates must hold a Ph.D., M.D., or equivalent degree, and have a strong track record during their graduate and postdoctoral career and a compelling vision for their future, independent research direction. The target starting date is August 16, 2013. The successful candidate will be located in the Department of **Molecular and Integrative Physiology** or the Department of **Cell and Developmental Biology** and will be expected to conduct independent research, perform academic duties associated with our BS and PhD programs, and have the ability to teach effectively at both the undergraduate and graduate levels. Salary is competitive and commensurate with experience. These positions offer excellent laboratory facilities, relocation start-up funds, and the opportunity to work with outstanding colleagues and graduate students.

Successful candidates would provide synergy with major campus research thrusts, particularly in cancer, stem cell and developmental biology, reproductive biology, and neurobiology. The Urbana-Champaign campus offers a wide range of state-of-the-art research support facilities that include the Roy J. Carver Biotechnology Center, the W. M. Keck Center for Comparative and Functional Genomics, as well as facilities for proteomics, metabolomics, high-throughput screening, immunology, flow cytometry, microscopy, and transgenic mice. The campus has strong programs in bioengineering, biological physics, and chemical biology, and superb computational resources are available at the National Center for Supercomputing Applications and the NIH Resource for Macromolecular Modeling and Bioinformatics.

Urbana-Champaign offers the residential advantages of a medium-sized university city, excellent cultural opportunities, and a high quality of life. In 2010, the University of Illinois at Urbana-Champaign received top rankings by Harvard University's Collaborative on Academic Careers in Higher Education for its pre-tenure practices in balancing work and home. (<http://www.insidehighered.com/news/2010/11/15/coache>)

To ensure full consideration, create your candidate profile through <http://go.illinois.edu/MCBAsstProf> and upload your application cover letter, curriculum vitae, a concise summary of past research accomplishments, a statement of future research plans and contact information for three professional references by **December 15, 2012**. Referees will be contacted electronically upon the submission of the application. Although early applications are appreciated and interviews may be conducted before the closing date, no hire will be made until after the closing date. Questions can be addressed to the School of Molecular and Cellular Biology, 217-333-3166.

*Illinois is an Affirmative Action /Equal Opportunity Employer and welcomes individuals with diverse backgrounds, experiences, and ideas who embrace and value diversity and inclusivity. ([www.inclusiveillinois.illinois.edu](http://www.inclusiveillinois.illinois.edu)).*



## Memorial Sloan-Kettering Cancer Center

*The Best Cancer Care. Anywhere.*

### FACULTY POSITIONS Center for Cell Engineering

The Center for Cell Engineering (CCE) at Memorial Sloan-Kettering Cancer Center is seeking innovative individuals with strong research accomplishments in stem cell research, cell engineering and/or cell therapy for tenure-track positions at the Assistant Member level.

Applicants may be considered for appointment in the Molecular Pharmacology and Chemistry, Immunology, Developmental Biology or Cancer Biology & Genetics Programs of the Sloan-Kettering Institute ([www.ski.edu](http://www.ski.edu)). Qualified applicants with an MD degree may be offered a joint appointment in an appropriate department in Memorial Hospital. Faculty will be eligible to hold appointments in the Gerstner Sloan-Kettering Graduate School of Biomedical Sciences, the Weill Cornell Graduate School of Medical Sciences, as well as the Tri-Institutional MD/PhD Training Program.

The CCE focuses on research leading to innovative cell therapies and their clinical translation. Successful applicants will have access to outstanding resources, including state-of-the-art facilities for cGMP cell processing, cell purification, cell imaging, vector production, sequencing, genomic analyses, chemical screens and immune monitoring. MSKCC offers a unique and exciting research environment with programs in Molecular Pharmacology & Chemistry, Developmental Biology, Immunology, Molecular Biology, Computational Biology, Cancer Biology & Genetics, Cell Biology, and Structural Biology. The presence on campus of world-renowned clinical programs in cancer research, treatment and prevention offer many opportunities for effective translational research.

Applicants should have an MD and/or PhD degree, productive postdoctoral experience, and dedication to important problems related to human cell engineering, including induced pluripotent stem cells, and the development of novel cell therapies.

The deadline for applications is November 1, 2012. Interested candidates should visit [facultysearch.ski.edu](http://facultysearch.ski.edu) to access the on-line faculty application. Please visit the site as soon as possible, as it contains important information on the required application materials, including deadlines for submission of letters of reference.

Inquiries may be sent to **Eden Bechard**, at [becharde@mskcc.org](mailto:becharde@mskcc.org) or to **Dr. Michel Sadelain**, Director, Center for Cell Engineering at [m-sadelain@ski.mskcc.org](mailto:m-sadelain@ski.mskcc.org).

### facultysearch.ski.edu

MSKCC is an equal opportunity and affirmative action employer committed to diversity and inclusion in all aspects of recruiting and employment. All qualified individuals are encouraged to apply.



SCHOOL OF MEDICINE & DENTISTRY  
UNIVERSITY OF ROCHESTER MEDICAL CENTER

### Tenure-Track/Tenured Faculty Position

The Center for Oral Biology in the Eastman Institute for Oral Health invites applications for a faculty position at the Associate or Full Professor level. Current research programs in the center include studies of the molecular mechanisms of craniofacial development and birth defects, salivary gland physiology and cell biology, organ development and regeneration, cellular signaling in cancer, and the molecular mechanisms of oral infectious diseases. We seek applications from individuals with research interests that will complement our existing programs, including but not limited to developmental genetics, stem cell and cancer biology, tissue engineering and repair, bacterial physiology/pathogenesis, regulation of mammalian gene expression, protein/glycoprotein interactions, and exocrine cell signaling/differentiation. More information about the center and available positions can be found on the internet (<http://www.urmc.rochester.edu/center-oral-biology/>).

Individuals seeking an appointment at the level of Associate or Full Professor must have a demonstrated record of extramural funding. For further details and to apply online, please go to: <http://www.rochester.edu/working/hr/jobs/> (Job ID #175946). Please provide your curriculum vitae, statement of current and future research interests, and names and addresses of at least three references.

*The University of Rochester is an Equal Opportunity Employer. Women and minorities are encouraged to apply.*

Maine Medical Center Research Institute (MMCRI) is a leading NIH-funded biomedical research institute and division of Maine Medical Center, a major academic affiliate of Tufts University School of Medicine.

### FACULTY POSITIONS AT MMCRI MAINE MEDICAL CENTER RESEARCH INSTITUTE Portland, Maine

Applications are invited for faculty positions at all levels (Assistant, Associate and Full Professor equivalent) in the Center for Molecular Medicine.

Candidates should complement existing strengths in the areas of stem cell biology, vascular and cardiovascular biology, metabolism, bone biology, cancer, and basic and translational studies of human disease. Applicants must have an MD and/or PhD degree or equivalent. Physician-scientists are encouraged to apply. Candidates for senior-level positions should have an independently funded research program. Applications are strongly encouraged from those seeking a highly supportive, collegial and collaborative environment.

Positions include competitive start-up/transition packages, and opportunities for faculty appointments at Tufts University School of Medicine and the University of Maine. MMCRI maintains core facilities in flow cytometry/FACS, mouse transgenic technologies, proteomics, bioinformatics support, confocal microscopy, metabolic phenotyping, small animal in vivo imaging including microCT and MRI, and translational and clinical research. Salary, benefits, and resources are nationally competitive.

MMCRI is an expanding biomedical research institute on the scenic southern coast of Maine. The greater Portland area features a high quality of life with outstanding recreational and cultural opportunities.

Candidates should provide a CV, brief statement of research interests, and contact information for three professional references to Tom Gridley PhD, Chair, Faculty Recruiting Committee ([gridt@mmc.org](mailto:gridt@mmc.org)). Learn more about us at [www.mmc.org](http://www.mmc.org).



Maine Medical Center  
Research Institute

We are an Equal Opportunity Employer.



FAS Center  
for Systems Biology



### Harvard University FAS Center for Systems Biology Faculty Position

The Faculty of Arts and Sciences (FAS) Center for Systems Biology (<http://sysbio.harvard.edu/csb>) seeks outstanding candidates for a faculty position at the rank of assistant professor (tenure track). The Center, whose common research space houses faculty from a spectrum of academic departments and the Bauer Fellows, fosters interactions across disciplinary boundaries. We are interested in candidates involved in research in systems biology, using either experimental or computational approaches. A PhD in a relevant discipline is required.

The successful candidate will hold an academic appointment in a FAS natural science department such as, but not restricted to, Molecular and Cellular Biology, Organismic and Evolutionary Biology, Physics or Chemistry and Chemical Biology. Faculty associated with the Center for Systems Biology have access to facilities and opportunities for collaborative research through the Bauer Core facilities, the Center for Nanoscale Systems, the Broad Institute, and the Center for Brain Science.

Applications, including letters of reference, are due by **November 15, 2012**. Please submit a curriculum vitae, statement of research (≤5 pages, including a summary of previous research accomplishments), teaching statement and PDFs of ≤3 publications to <http://academicpositions.harvard.edu/postings/4214>. All files must be submitted electronically in PDF or Word format. During the application process you will be asked to give the e-mail addresses of at least three colleagues who have agreed to write letters of recommendation for you. Please allow at least 1 week for your referees to upload their letters.

*Applications from, or nominations of, women and minority candidates are encouraged. Harvard is an Affirmative Action/Equal Opportunity Employer.*





Memorial Sloan-Kettering  
Cancer Center

*The Best Cancer Care. Anywhere.*

## FACULTY POSITIONS

### Center for Stem Cell Biology & Developmental Biology Program

The Center for Stem Cell Biology (CSCB) and the Developmental Biology Program are seeking innovative individuals who have strong records of research accomplishments in stem cell biology for tenure-track positions at the Assistant Member level (equivalent to Assistant Professor). The CSCB was established to further the interaction of researchers with active stem cell research programs at the Center, to enhance and build novel stem cell related resources and to recruit leading-edge stem cell faculty. The CSCB is interested in research in any aspect of stem cell biology, including the study of stem cells in model organisms, tissue stem cells and the biology and application of human embryonic stem cells or induced pluripotent stem cells. Candidates with a strong interest in applying developmental approaches to studying stem cell biology are particularly encouraged to apply.

Applicants should have a PhD and/or MD degree, a productive postdoctoral experience, dedication to important problems in stem cell biology, and the potential to develop a strong independent program in stem cell research. Successful candidates will be appointed in the Developmental Biology Program and will become a member of the CSCB. Successful candidates are also eligible to hold additional appointments at the Gerstner Sloan-Kettering Graduate School of Biomedical Sciences, the Weill Cornell Graduate School of Medical Sciences, as well as the Tri-Institutional MD/PhD Training Program.

Successful applicants will have access to outstanding resources including expanded state-of-the-art facilities for human pluripotent stem cells, high-throughput chemical and genetic screening, mouse genetics, genomics, flow cytometry, advanced imaging and cancer biology. Memorial Sloan-Kettering offers a unique and exciting multidisciplinary research environment. Faculty in the CSCB participate in the Tri-Institutional stem cell initiative (with Weill Cornell and Rockefeller University) that links stem cell researchers across neighboring institutions.

The deadline for applications is **November 1, 2012**. Interested candidates should visit [facultysearch.ski.edu](http://facultysearch.ski.edu) to access the on-line faculty application. The site contains important information on the required application materials as well as deadlines for submission of letters of reference.

Inquiries may be sent to **Tiffany Lennon** at [lennont@mskcc.org](mailto:lennont@mskcc.org); to **Dr. Lorenz Studer, Director CSCB**, at [studerl@mskcc.org](mailto:studerl@mskcc.org); or to **Dr. Kathryn Anderson, Chair Developmental Biology Program**, at [k-anderson@ski.mskcc.org](mailto:k-anderson@ski.mskcc.org).

**facultysearch.ski.edu**

MSKCC is an equal opportunity and affirmative action employer committed to diversity and inclusion in all aspects of recruiting and employment. All qualified individuals are encouraged to apply.



UMASS  
AMHERST

## Two Tenure-Track Assistant Professor Positions Department of Biology

The Biology Department ([www.bio.umass.edu/biology](http://www.bio.umass.edu/biology)) at the University of Massachusetts Amherst invites applications for two tenure-track Assistant Professor positions to start as soon as September 1, 2013. One position is in the area of **Neurobiology** and the other is in the area of **Evolutionary Developmental Biology of Plants**.

We seek individuals with outstanding research, a strong commitment to teaching, and the potential to develop and maintain an extramurally funded research program. The Biology Department provides an interactive and broad research environment, with faculty research spanning all levels of biological organization. Especially strong research clusters focus on nervous system development and function, plant biology, cell biology, functional morphology, and evolution. New faculty members will have the opportunity to participate in strong graduate training programs in Neuroscience and Behavior ([www.umass.edu/neuro](http://www.umass.edu/neuro)), Plant Biology ([www.bio.umass.edu/plantbio](http://www.bio.umass.edu/plantbio)), Organismic and Evolutionary Biology ([www.bio.umass.edu/oeb](http://www.bio.umass.edu/oeb)) and Molecular and Cellular Biology ([www.bio.umass.edu/mcb](http://www.bio.umass.edu/mcb)). A PhD in Biology or a related field and postdoctoral experience are required.

**1) Neurobiology:** We seek individuals with a strong record of research in the area of neurobiology. We particularly welcome applications from researchers working in the areas of neural degeneration, neural development, or other aspects of long-term change in neuronal function, but strongly encourage applications from researchers working in other areas as well. Application materials may be sent via email to: [NeurobiologySearch@bio.umass.edu](mailto:NeurobiologySearch@bio.umass.edu).

**2) Plant Evolutionary/Developmental Biology (Evo/Devo):** We seek individuals with a strong record of research at the interface between developmental and evolutionary biology. Applications are welcome from candidates pursuing questions at any phylogenetic level, from the origins and mechanisms of evolutionary novelty to the significance of phenotypic variation in any group of plants. UMass is home to a diverse live plant collection containing nearly 700 genera from more than 225 families that can be used for teaching and research. Application materials may be sent via email to: [PlantEvoDevoSearch@bio.umass.edu](mailto:PlantEvoDevoSearch@bio.umass.edu).

The University is part of the 5 College Consortium ([www.fivecolleges.edu](http://www.fivecolleges.edu)) in the beautiful Pioneer Valley in western Massachusetts, just 2 hours from Boston and 3 hours from New York City.

If needed, paper applications can be sent to: Neurobiology Search # R44072, or PlantEvoDevo Search # R44071, Biology Department, Attn: Zoe Crowley, 611 North Pleasant Street, University of Massachusetts, Amherst, MA 01003. Application materials should include a curriculum vitae, research plan, and teaching statement. Applicants should also have three reference letters sent to the addresses above. Evaluation of applications for both positions will begin on October 5, 2012 and continue until the positions are filled.

*The University provides an intellectual environment committed to providing academic excellence and diversity including mentoring programs for faculty. The College of Natural Sciences and the Biology Department are committed to increasing the diversity of the faculty, student body, and the curriculum. We strongly encourage women and members of minority groups to apply.*

*The University of Massachusetts is an Affirmative Action/Equal Opportunity Employer. Positions will be filled contingent upon University funding.*



## Memorial Sloan-Kettering Cancer Center

*The Best Cancer Care. Anywhere.*

### FACULTY POSITION Structural Biology Program

The Structural Biology Program of the Sloan-Kettering Institute ([www.ski.edu](http://www.ski.edu)) invites applications for a tenure-track faculty position at the Assistant Member level (equivalent to Assistant Professor). We are interested in individuals who have an outstanding record of research accomplishments. Areas of interest include x-ray crystallography, NMR spectroscopy, EM and optical imaging, as well as the interface of structural, chemical and computational biology. Faculty will be eligible to hold graduate school appointments in the Gerstner Sloan-Kettering Graduate School of Biomedical Sciences, the Weill Cornell Graduate School of Medical Sciences, as well as the Tri-Institutional MD/PhD Training Program.

The deadline for applications is November 1, 2012. Interested candidates should visit <http://facultysearch.ski.edu> to access the on-line faculty application. Please visit the site as soon as possible, as it contains important information on the required application materials, including deadlines for submission of letters of reference.

Informal inquiries may be sent to **Julie Kwan** at [kwanj@mskcc.org](mailto:kwanj@mskcc.org) or to **Dr. Nikola Pavletich**, **Chair, Structural Biology Program** at [pavletin@mskcc.org](mailto:pavletin@mskcc.org).

**facultysearch.ski.edu**

MSKCC is an equal opportunity and affirmative action employer committed to diversity and inclusion in all aspects of recruiting and employment. All qualified individuals are encouraged to apply.



## CHILDREN'S MEDICAL CENTER RESEARCH INSTITUTE AT UT SOUTHWESTERN

### Faculty Position in Cancer Biology

The Children's Research Institute (CRI) at the University of Texas-Southwestern Medical Center in Dallas, TX seeks applications for a **tenure-track faculty position in the area of cancer biology**. Outstanding investigators at any rank will be considered. Candidates must have a Ph.D., M.D. or equivalent degrees and the ability to direct an independently-funded research program exploring any aspect of cancer biology.

The UT-Southwestern Medical Center has a long and distinguished history of excellence in disease-related basic science research. The CRI is a new institute recruiting outstanding individuals dedicated to solving fundamental problems in biology and disease. The CRI is a dynamic, stimulating, and highly collaborative scientific environment. Major areas of focus within the CRI will include stem cell biology, cancer biology, and metabolism.

Please submit a CV, a 2-page summary of past accomplishments and research plans, and ask three references to submit letters by **November 1, 2012** to [CRIApplicants@utsouthwestern.edu](mailto:CRIApplicants@utsouthwestern.edu).

*UT Southwestern is an Equal Opportunity/  
Affirmative Action Employer.*

**SFU**

SIMON FRASER UNIVERSITY  
ENGAGING THE WORLD

Simon Fraser University is one of Canada's best comprehensive universities with three campuses in Metro Vancouver. Through the strength and commitment of our staff and faculty, SFU is recognized as a top employer in both B.C. and Canada. We invite applications for the following position:

### DEPARTMENT OF CHEMISTRY FACULTY POSITION IN CHEMISTRY

The Department of Chemistry at Simon Fraser University (SFU) invites applications for a tenure-track Assistant Professor position in Bio-Physical or Materials Chemistry to take effect in September 2013, subject to final budgetary approval.

Applicants should have a Ph.D. degree and will normally have postdoctoral or industrial experience. Outstanding candidates with a commitment to excellence in research and teaching are being sought. The candidates will be expected to develop and maintain both an innovative, externally funded research program, and an excellent teaching record at both the undergraduate and graduate levels in Chemistry.

All qualified candidates are encouraged to apply; however, Canadians and Permanent Residents will be given priority. Simon Fraser University is committed to an equity employment program that includes special measures to achieve diversity among its faculty and staff and welcomes applications from all qualified individuals. We therefore particularly encourage applications from qualified women, aboriginal Canadians, persons with disabilities, and members of visible minorities. Applicants should send a complete résumé, a concise research proposal, a short teaching dossier, and a list of three individuals willing to act as referees with their addresses, telephone and/or fax numbers, and e-mail addresses. All correspondence should be sent to:

Dr. Zuo-Guang Ye, Professor and Chair, Department of Chemistry  
Simon Fraser University, 8888 University Drive, Burnaby BC V5A 1S6 Canada  
E-mail: [chemchr@sfu.ca](mailto:chemchr@sfu.ca)

The competition will remain open until the position is filled. Screening of applications will commence on November 1, 2012.

Please note: We thank all applicants for their interest, however, only those selected for interviews will be contacted.

Please note that under the University Act, personal information that is required by the University for academic appointment competitions will be collected. For further details see the Collection Notice.  
([www.chemistry.sfu.ca/about/employment](http://www.chemistry.sfu.ca/about/employment))

**[www.sfu.ca/jobpostings](http://www.sfu.ca/jobpostings)**

## SOUTHWESTERN THE UNIVERSITY OF TEXAS SOUTHWESTERN MEDICAL CENTER AT DALLAS

### Assistant Professor in Human Genetics

The Center for Human Genetics (McDermott Center) at The University of Texas Southwestern Medical Center at Dallas (<http://www.utsouthwestern.edu/education/medical-school/departments/mcdermott-center/index.html>) invites applications for a tenure-track position of Assistant Professor. We are seeking individuals with innovative experimental research programs in human molecular genetics. Successful applicants will be expected to establish a vigorous independent research program and to teach students at the graduate level.

The individual should hold a graduate degree (MD, PhD or MD/PhD) and have completed a post-doctoral fellowship. The appointment will include a competitive salary, attractive start-up package, excellent laboratory space in a dynamic research environment with access to the Center's state-of-the-art infrastructure for basic and clinical research related to human genetics, including next-generation sequencing and bioinformatics cores. The faculty member will have a joint appointment in a basic science or clinical department. Applicants should submit their curriculum vitae containing a summary of past accomplishments, a statement of future objectives, and three professional references to:

**Faculty Search Committee**  
**c/o Susan Hayes, Dept. Administrator**  
**McDermott Center for Human Growth and Development**  
**UT Southwestern Medical Center at Dallas**  
**5323 Harry Hines Boulevard**  
**Dallas, Texas 75390-8591**

Or by email to: [Susan.Hayes@UTSouthwestern.edu](mailto:Susan.Hayes@UTSouthwestern.edu)

*UTSW is an Equal Opportunity Employer.  
Women and Minorities are encouraged to apply.*



**School of the Environment  
Assistant Professor (2 positions)**

**Quantitative Spatial Ecologist  
Position #115990**

**Aquatic/Riparian Ecologist  
Position #79388**

Washington State University (WSU) is currently seeking to fill two tenure-track Assistant Professor positions in the areas of Quantitative Spatial Ecology and Aquatic/Riparian Ecology. These positions are full-time, 9-month faculty positions located on the Pullman Campus. These positions are part of a multi-year series of new hires intended to contribute to the growth and development of the new School of the Environment, a new, innovative and interdisciplinary academic unit at WSU that brings together the natural and social sciences to focus on Earth, ecosystems, and sustainability. The School of the Environment (SoE) has identified the following thematic areas around which to build: 1) "Water: Connecting Earth and Life," 2) "Global Change: Sustaining Healthy Landscapes and Communities," and 3) "Earth System Dynamics." Responsibilities include developing and teaching undergraduate and graduate courses and mentoring MS and PhD graduate students. SoE has a single faculty and a common curriculum across the Pullman, Tri-Cities and Vancouver campuses of the WSU System.

The **Quantitative Spatial Ecologist** will develop an internationally recognized research program in quantitative spatial ecology, with expertise in applied ecological modeling, potentially including genetic and/or temporal analyses. Specific habitats and taxa of emphasis are open, but candidates with expertise in vertebrate populations and ecological communities on the landscape scale are particularly encouraged to apply. The successful applicant will be expected to conduct an approved program of research consistent with the missions of the WSU Agricultural Research Center.

**Required:** Earned doctorate in a discipline related to quantitative spatial ecology, at time of employment. Record of research accomplishment as demonstrated by peer-reviewed publications and/or extramural grantsmanship. Demonstrated ability and/or potential to successfully teach and mentor students at the graduate and undergraduate levels. **Preferred:** Demonstrated ability in statistical and spatial analysis; demonstrated effective oral and written communication skills; demonstrated ability to develop collaborations with colleagues within and outside of home School and Colleges, helping to further integrate the School into University-wide focal areas; ability to work with a variety of constituencies, including governmental agency representatives, and persons of diverse cultures and backgrounds. For questions about this position contact **Lisa Shipley, 509-335-9182, shipley@wsu.edu**.

The **Aquatic/Riparian Ecologist** will develop an internationally recognized research program in aquatic and/or riparian ecology. Although the specific habitat(s) and area of emphasis are open, candidates with expertise in linking biological processes with physical processes (e.g., via hydrology, fluvial geomorphology, biogeochemistry, sediment transport, or climate dynamics) are particularly encouraged to apply. **Required:** Earned doctorate in a discipline related to aquatic or riparian ecology, at time of employment; record of research accomplishment as demonstrated by peer-reviewed publications and/or extramural grantsmanship; demonstrated ability and/or potential to successfully teach and mentor students at the graduate and undergraduate levels. **Preferred:** Demonstrated ability to develop collaborations with colleagues within and outside of home School and Colleges, helping to further integrate the School into University-wide focal areas; ability to work and communicate with a variety of constituencies, including governmental agency representatives, and persons of diverse cultures and backgrounds. For questions about the position contact **Kent Keller, 509-335-3040, ckeller@wsu.edu**.

Screening begins **November 13, 2012**. To apply for either of the searches visit: <https://www.wsujobs.com>. Application materials must include a letter describing how your experience and training meet qualifications for the position, a research plan, a statement of teaching philosophy, current vitae, and names and contact information for three professional references.

EEO/AA/ADA



**Faculty Positions in  
Continental Margins  
and Coastal Environments**

Scripps Institution of Oceanography (SIO) at UC San Diego (<http://sio.ucsd.edu>) is committed to academic excellence and diversity within the faculty, staff, and student body. SIO is a world renowned center of marine research with approximately 200 principal investigators leading research programs on all aspects of earth, ocean and atmospheric sciences.

**Coastal Processes #10-439:** We seek outstanding candidates with complementary interests in the physical oceanography of the coastal environment. Topics of interest are focused on the shelf, inner shelf, and near shore, including tidal inlets, estuaries, river mouths, beaches, and headlands. Some examples of physical interest are: surf zone processes; surf zone-inner shelf exchange; sediment, chemical, and biological transport; waves (internal and surface); and coastal response to sea level changes or human activity.

**Coastal Ecology #10-440:** We seek outstanding candidates with expertise in the biology and ecology of the coastal environment. Areas of interest broadly include the interactions of marine organisms with one another and with their physical and chemical environment. Research topics may include the ecology of benthic and pelagic organisms, ecological processes and regulatory mechanisms, population recruitment and connectivity, response to habitat changes and disruptions, bio(geo)chemistry and genomic adaptation. Research programs that integrate observational, experimental and modeling approaches in the field and laboratory are encouraged.

**Geological, Geophysical and Geochemical Studies of Continental Margins #10-441:** We seek outstanding candidates from throughout the Earth sciences with complementary skills targeting continental margin development, evolution, and physical/chemical exchange across a variety of spatial and temporal scales. An emphasis on the marine portion of the system is envisioned, but candidates investigating onshore aspects of margin processes that cross the shoreline will also be considered. We encourage applicants whose research bears on key processes at margins, including geochemistry, geophysics, dynamics, seismology, tectonics, structural geology, geodesy, petrology, geochemical exchange (high- and low-temperature), geomorphology, glaciology, and ice-margin studies.

All successful candidates will be expected to teach classes, supervise research at both the graduate and undergraduate level and contribute to leadership on issues of equity and diversity. The positions require a PhD degree and a competitive record of publication, as well as evidence of the ability to conduct and fund an active research program consistent with the opportunity to have done so at this career level. The successful candidates will also have demonstrated the highest standards of scholarship and professional activity, or for junior scholars to have the potential thereof. The department is interested in candidates who have demonstrated commitment to excellence by providing leadership in teaching, research or service towards building an equitable and diverse scholarly environment.

Our preference is for hiring at the level of assistant professor for all positions, however appointments at all ranks may also be considered. Salary will depend on the experience of the successful applicant and will be based on the UCSD pay scales. Completed applications received by **October 15, 2012** will be assured of consideration. Each position requires separate submission. All applications and related materials must be submitted electronically via Academic Personnel On-Line RECRUIT at: (<https://apol-recruit.ucsd.edu>). Emailed applications will not be accepted. Applicants should provide a current CV, cover letter including descriptions of their teaching experience, research interests, state if authorized to work in the U.S., and the names of three potential referees, along with their complete institution address, email address, phone and fax numbers, and a separate personal statement summarizing past or potential contributions to diversity (see <http://facultyequity.ucsd.edu/Faculty-Applicant-C2D-Info.asp> and <http://sio.ucsd.edu/Diversity/> for further information). Questions about submission of applications may be addressed to **Leslie Costi, (lcosti@ucsd.edu)**.

*UCSD is an Affirmative Action/Equal Opportunity Employer with a strong institutional commitment to excellence through diversity.*





**FACULTY POSITIONS in TYPE 1 DIABETES  
SANFORD PROJECT/CHILDREN'S HEALTH RESEARCH CENTER  
SANFORD RESEARCH/USD**

The Sanford Project, a major multidisciplinary research initiative and part of the Children's Health Research Center (CHRC, Sioux Falls, SD <http://www.sanfordresearch.org/researchcenters/childrenshealth/>), invites applications from researchers for full time faculty positions at the rank of Associate Scientist, Scientist, and Senior Scientist within Sanford Research/USD (<http://www.sanfordresearch.org/>) with commensurate rank of Assistant Professor, Associate Professor, and Full Professor in the Department of Pediatrics of the Sanford School of Medicine at The University of South Dakota. An historic \$400 million gift by philanthropist Denny Sanford has allowed for expansion of Sanford Research/USD and provided for the establishment and dynamic development of The Sanford Project, the cutting-edge academics-to bedside research initiative specifically focused on finding and delivering modern therapies for Type 1 Diabetes.

We seek outstanding scientists to improve the understanding and treatment of diabetes. Areas of interest include beta cell biology, immunology, genetics, development and beta cell regeneration with a particular focus on translational approaches. Applicants should hold a PhD, MD or MD/PhD degree and complement the existing strengths and the interdisciplinary and collaborative nature of the CHRC. Junior candidates will be expected to develop independent research programs with extramural funding. Senior candidates should have a demonstrated track record of extramural grant support and publications and be capable of providing mentorship to junior faculty members within the CHRC while advancing their independent research programs. Researchers will join an energetic and collegial research community and hold both Sanford Research and Sanford School of Medicine faculty appointments.

Significant institutional support, including modern laboratory space and state-of-the-art facilities, will be provided in the Sanford Center. In addition, a comprehensive compensation package will be tailored to the individual's qualifications. Sanford Health is an Equal Opportunity/Affirmative Action Employer. Candidates should submit a single PDF including a detailed *curriculum vitae*, a description of research experience and future plans. Candidates should also submit at least three letters of recommendation. All application materials should be sent by email to: **David A Pearce Ph.D., Director, Children's Health Research Center, Sanford Research/USD, Professor, Department of Pediatrics, Sanford School of Medicine of The University of South Dakota, 2301 E. 60<sup>th</sup> Street North, Sioux Falls, SD 57104; Telephone: 605-312-6004 FAX: 605-312-6071; Email: [David.Pearce@sanfordhealth.org](mailto:David.Pearce@sanfordhealth.org).**



**RICE**

**RICE UNIVERSITY  
FACULTY SEARCH  
Biochemistry and  
Cell Biology  
Rice University in  
Houston, TX  
<http://www.rice.edu/>**

Applications are invited for an anticipated faculty position, at a rank to be determined, in broad areas of biological research including biochemistry, cell and developmental biology, and systems and synthetic biology. Applicants using experimental and/or computational approaches that intersect with chemistry, physics, or engineering are encouraged to apply. Candidates must have a Ph.D., postdoctoral training, and outstanding potential in research and teaching. Successful candidates are expected to develop and maintain a vigorous research program supported by extramural funding and participate in graduate and undergraduate education. Review of applications will commence **October 15, 2012** and continue until the position is filled.

Please compile a PDF containing a cover letter, curriculum vitae, summary of past research, and statement of future research plans and email to [BCBSearch@rice.edu](mailto:BCBSearch@rice.edu). Arrange for four letters of reference to be sent to the same email address.

*Rice University is an Equal Opportunity/Affirmative Action Employer; women and minority candidates are especially encouraged to apply.*



**CHILDREN'S MEDICAL CENTER  
RESEARCH INSTITUTE  
AT UT SOUTHWESTERN**

**Faculty Position in Metabolism Research**

The Children's Research Institute (CRI) at the University of Texas-Southwestern Medical Center in Dallas, TX seeks applications for a **tenure-track faculty position in the area of metabolism and disease**. Outstanding investigators at any rank will be considered. Candidates must have a Ph.D., M.D. or equivalent degrees and the ability to direct independently-funded research programs. Areas of specific interest include analysis of metabolism at the cellular level, including metabolomics, metabolic flux analysis, metabolic imaging and mitochondrial biology. In addition to analytical equipment dedicated to the investigator's studies, CRI members will also have access to a metabolomics core with triple-quadrupole mass spectrometry and gas chromatography/mass spectrometry. NMR spectroscopy, <sup>13</sup>C dynamic nuclear polarization, a human 7-Tesla MRI and a state-of-the-art mouse metabolic phenotyping facility are also available on campus to provide an unparalleled breadth of metabolic analysis.

The UT-Southwestern Medical Center has a long and distinguished history of excellence in disease-related basic science research. The CRI is a new institute recruiting outstanding individuals dedicated to solving fundamental problems in biology and disease. The CRI is a dynamic, stimulating, and highly collaborative scientific environment. Major areas of focus within the CRI will include stem cell biology, cancer biology, and metabolism.

Please submit a CV, a 2-page summary of past accomplishments and research plans, and ask three references to submit letters by **November 1, 2012** to [CRIApplicants@utsouthwestern.edu](mailto:CRIApplicants@utsouthwestern.edu).

*UT Southwestern is an Equal Opportunity/Affirmative Action Employer.*



**Yale School of Forestry & Environmental Studies  
Junior or Senior Faculty Position in  
Tropical Forest Management**

The Yale School of Forestry & Environmental Studies has an open rank, tenure-track opening for an exceptional natural scientist whose research focuses on the conservation and management of tropical forest resources. Ideal candidates will conduct interdisciplinary, field-based, hypothesis-driven research that bridges the social and biophysical sciences. They will also demonstrate potential for collaborating with natural, physical and social scientists at Yale and within a strongly interdisciplinary School. Areas of research could include: the science, policy and management of forest resources; biodiversity; climate-change related interventions; and the intersection between forest resource management, agriculture and land use. The ability to develop student field experiences, teach classes, and conduct research in both temperate and tropical systems would be an asset.

The successful candidate will be expected to develop an internationally recognized research program, and will teach introductory and advanced classes in the Yale School of Forestry & Environmental Studies and also in Yale College.

Applicants should submit a curriculum vitae, a statement of research and teaching interests, and the names of four references via email with the subject line "Environment Faculty Searches - Tropical Forest Management" to [fesdeansoffice@yale.edu](mailto:fesdeansoffice@yale.edu) or via surface mail to: **Tropical Forest Management Faculty Search, c/o Angela Kuhne, Dean's Office, Yale School of Forestry & Environmental Studies, 195 Prospect Street, New Haven, CT 06511, USA.**

Prior to applying, candidates should explore the School's website ([www.environment.yale.edu](http://www.environment.yale.edu)) and consider how their expertise can strengthen or complement the strengths of the existing faculty of the School. Applications received by **October 5, 2012** will receive full consideration. For more information about the position, contact **Assistant Dean Angela Kuhne** at [angela.kuhne@yale.edu](mailto:angela.kuhne@yale.edu).

*Yale University is an Affirmative Action/Equal Opportunity Employer.  
Men and women of diverse racial/ethnic backgrounds and cultures are encouraged to apply.*

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### **APPLICATION DEADLINE:**

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**Tier 2 Canada Research Chair in Chemical Biology**  
**Schulich School of Medicine & Dentistry and Faculty of Science**  
**Western University**



The Schulich School of Medicine & Dentistry and the Faculty of Science at Western University, one of Canada's leading research intensive universities, seek applicants for a Tier 2 Canada Research Chair (CRC) in Chemical Biology. In accordance with the regulations set for Tier 2 Canada Research Chairs ([www.chaires-chaire.gc.ca/home-accueil-eng.aspx](http://www.chaires-chaire.gc.ca/home-accueil-eng.aspx)), the candidate will be an excellent emerging researcher who has demonstrated research creativity and innovation, and the potential to achieve international recognition in the field of Chemical Biology within the next five to ten years.

The Tier 2 CRC will be expected to establish an independent, externally funded research program in the area of Chemical Biology that will promote integration and synergy with existing areas of research strength in Proteomics & Protein Structure, Genomics & Bioinformatics, Synthesis and/or Materials & Biomaterials within the Schulich School of Medicine & Dentistry and the Faculty of Science at Western. Priority will be given to candidates with a strong record of productivity in chemical biology and interests in translational research. The candidate will have access to state-of-the-art facilities including the London Regional Proteomics Centre ([www.lrpc.uwo.ca](http://www.lrpc.uwo.ca)), the London Regional Genomics Centre ([www.lrgc.ca](http://www.lrgc.ca)) and the Western Nanofabrication Facility (<http://www.uwo.ca/fab/>). Furthermore, there will be excellent opportunities for collaboration with basic and clinical researchers at UWO and affiliated research institutes.

The successful applicant will hold a Ph.D. or an M.D., or equivalent, and will be a tenure track appointment at the position of Assistant Professor or at an Associate Professor level if qualifications and experience warrant. The appointment will be made to the Department of Biochemistry of Schulich School of Medicine & Dentistry and the Department of Chemistry of the Faculty of Science, with the opportunity for a cross-appointment to an appropriate Clinical Department, and an appointment as Scientist at the Robarts Research Institute and Lawson Health Research Institute.

With full time enrollment of about 32,000, The Western University graduates students from a range of academic and professional programs. Further information about the Schulich School of Medicine & Dentistry can be found at [www.schulich.uwo.ca](http://www.schulich.uwo.ca), the Faculty of Science at [www.uwo.ca/sci](http://www.uwo.ca/sci) and/or at [www.uwo.ca](http://www.uwo.ca). Western's Recruitment & Retention Office is available to assist in the transition of the successful applicant and his or her family.

The application should include a detailed curriculum vitae, a brief description of research accomplishments, representative publications, and the names of three references. As well, the candidate must include a proposal for an original, innovative, and high quality research program that would attract excellent trainees, students, and future researchers. Please send the complete application to:

**Dr. Denise Figlewicz**  
**Vice Dean, Research & Innovation, Schulich School of Medicine & Dentistry**  
**Robarts Research Institute, Room 1240A**  
**Western University**  
**London, Ontario CANADA N6A 5C1**  
[selection.committee@schulich.uwo.ca](mailto:selection.committee@schulich.uwo.ca)

Applications will be accepted until the position is filled. Review of applicants will begin after **November 1, 2012**.

*Positions are subject to budget approval. Applicants should have fluent written and oral communication skills in English. All qualified candidates are encouraged to apply; however, Canadians and permanent residents will be given priority. Western University is committed to employment equity and welcomes applications from all qualified women and men, including visible minorities, aboriginal people and persons with disabilities.*



## The University of Iowa Department of Biology

The Department of Biology at the University of Iowa invites applications for an Assistant/Associate Professor position in the area of Genetics. Of particular interest are candidates whose research focuses on key genetic processes. These include, but are not limited to: DNA replication; transcription; translation; gene regulation; DNA repair and/or recombination; mutation and genome stability; and chromosome structure and behavior. Candidates using established genetic model systems and multifaceted approaches such as combinations of genetic, genomic, computational and molecular techniques are especially encouraged to apply. Candidates should have a clear interest in the Biology Department's teaching mission, which includes teaching undergraduate courses in Genetics.

Applicants must have a Ph.D. in Genetics or a related discipline and relevant postdoctoral experience. Candidates at the Assistant Professor level should have a strong publication record and the ability to obtain extramural support. Candidates at the Associate Professor level should have experience as an Assistant Professor (or equivalent), a strong publication record, an international reputation, and a history of successful extramural funding.

The successful candidate will be expected to interact with the current Genetics group in the Department of Biology and participate in the innovative campus-wide "Genetics Cluster". The Cluster is a University initiative that is designed to complement current expertise on campus in Genetics and promote interactions and collaborative research among Geneticists from several departments and colleges. Participation in the Genetics Cluster will be an important component in performance evaluations. An existing Interdisciplinary Genetics Graduate Program provides additional opportunities for interactions with graduate students and other Geneticists.

Applications should be submitted online at <http://jobs.uiowa.edu> under requisition number **61394**. Applicants must provide a cover letter, *curriculum vitae*, statement of research objectives, statement of teaching experience and interests, no more than 4 relevant publications, and the names of three references. Formal screening of applications will begin on **October 1, 2012** and continue until the position is filled.

*The Department and the College of Liberal Arts and Sciences are strongly committed to gender and ethnic diversity. The University is an Affirmative Action/Equal Opportunity employer. Women and minorities are encouraged to apply.*



## Faculty Position Center for Cell and Genome Science and the Department of Biology

The Center for Cell and Genome Science and the Department of Biology invite applications for a tenure-track faculty position in Biology at the Assistant Professor level; applications from more senior scientists will be considered as well. We are seeking a creative and independent person working in any area of cell biology or genome science who is pursuing quantitative, mechanistic approaches to fundamental problems in cell biology, including the development or application of novel experimental methods in imaging or genomics. The successful applicant will be expected to maintain a vigorous independent research program and contribute to teaching. The new faculty member will be provided with outstanding infrastructural support as a member of the Center for Cell and Genome Science with a primary appointment in the Department of Biology, and will also have access to graduate students from programs in Biology, Chemistry, Physics, Molecular Biology, Biological Chemistry and Neuroscience.

Candidates must hold a Ph.D. degree or equivalent, preferably in Biology, Chemistry, Biophysics or Biological Chemistry. Review of applications will commence **November 1, 2012** and will continue until the position is filled. Application for this position can be made at <http://utah.peopleadmin.com/postings/9082>.

*The University of Utah is an Equal Opportunity/Affirmative Action Employer and Educator. Minorities, women, and persons with disabilities are strongly encouraged to apply. Veterans preference. Reasonable accommodations provided. For additional information: <http://www.regulations.utah.edu/humanResources/5-106.html>. The University of Utah values candidates who have experience working in settings with students from diverse backgrounds, and possess a strong commitment to improving access to higher education for historically underrepresented students.*



## University of Missouri EVOLUTIONARY BIOLOGY Faculty Position Assistant or Associate Professor Division of Biological Sciences



The Division of Biological Sciences (<http://biology.missouri.edu>) at the University of Missouri invites applications for an Assistant or Associate Professor in evolutionary biology. We are interested in candidates studying the processes of evolution, broadly defined, with research programs that form linkages to our current faculty. The campus strengths in life sciences include behavior, genetics, ecology, neurobiology, genomics, bioinformatics, and anthropology. The successful candidate will establish a research program that complements our existing strengths, develops cross-disciplinary collaborations, and attracts federal funding.

We offer a highly competitive salary and start-up package, an active doctoral program with institutional support for students, and a highly interactive faculty. Columbia, Missouri, is ranked among the top-ten best college towns in the U.S. *We are committed to ethnic, racial and gender diversity in our faculty and strongly encourage applications from women and members of groups underrepresented in mathematics and science.*

Review of application materials (cover letter, CV, description of research plans and teaching interests, and contact information for three references, all compiled into a single PDF file) will begin **October 15, 2012**. Application submission instructions can be found at <http://biology.missouri.edu/evosearch>. Questions should be addressed to [evosearch@missouri.edu](mailto:evosearch@missouri.edu).

*Equal Employment Opportunity: The University of Missouri is an Equal Access, Equal Opportunity, Affirmative Action Employer that is fully committed to achieving a diverse faculty and staff. For more information, call the Associate Vice Chancellor of Human Resource Services/Affirmative Action officer at 573-882-4256. To request ADA accommodations, please call Human Resource Services at 573-882-7976. TTY users, please call through Relay Missouri, 1-800-RELAY (735-2966) or en Español at 1-800-520-7309.*



## TEXAS TECH UNIVERSITY

### Department of Chemistry and Biochemistry

The department of Chemistry and Biochemistry (<http://www.depts.ttu.edu/chemistry/>) invites applications for tenure-track positions (open rank) in the area of **Chemical Biology**. The successful candidates will establish a strong independent research program in drug discovery and development or other areas of chemistry applied to biology, including the plant sciences. Areas of specialization are open, but should complement the interests of a new program in Chemical Biology and institutional strategies adopted by Texas Tech University to foster interdisciplinary research in cancer, infectious diseases, synthetic chemistry and plant biology. Competitive candidates will have evidence to generate (junior hire) or maintain (senior hire) a well-funded research program. A demonstrated commitment to excellence in teaching and service are essential. The Department of Chemistry and Biochemistry is among the top academic units at Texas Tech University, in terms of research funding, publications and graduate education. Texas Tech University is classified as a doctoral research-extensive university by the Carnegie Foundation and has recently qualified to receive funding from the State of Texas National Research University Fund. It has an enrollment of more than 32,000 students, and is one of the major, state-supported, multidisciplinary universities of the Southwest. A School of Medicine is located on the main campus in Lubbock.

*All applications must be submitted online.* Online faculty application for **requisition number 86749** can be found at <http://jobs.texasstate.edu>. Applications must include a curriculum vita, statement of proposed research and teaching philosophy, and for applicants at the Assistant or Associate Professor level must also arrange to have three confidential letters of recommendation sent on their behalf, directly to **Dr. W. David Nes, Chair of Chemical Biology Search Committee, Department of Chemistry and Biochemistry, Texas Tech University, Box 41061, Lubbock, TX 79409-1061** ([wdavid.nes@ttu.edu](mailto:wdavid.nes@ttu.edu)). Evaluation of applications will begin on **October 15, 2012**, and continue until the positions are filled.

*Texas Tech University is an Affirmative Action/Equal Opportunity Employer, committed to excellence through diversity. Texas Tech welcomes applications from minorities, women, veterans, persons with disabilities, dual-career couples, and all qualified persons.*





**Brown University**  
**Molecular Toxicology/Environmental Carcinogenesis**  
**Open Rank Faculty Position**

Applications with outstanding research accomplishments are invited for an open rank faculty position (tenure-track Assistant Professor, tenured Associate or Full Professor) in the Department of Pathology and Laboratory Medicine at the Warren Alpert Medical School of Brown University. Appointments at the senior levels require a successful track record of peer-reviewed funding and a national (Associate Professor) or international (Full Professor) reputation. Strong commitment to teaching and mentoring is expected. Applicants must have a Ph.D., Sc.D., and/or M.D. degree and postdoctoral research experience. Applicants should have a laboratory-based research program in molecular mechanisms of environmentally-induced disease. The appointee will participate in undergraduate, graduate and/or medical teaching and mentoring. Research space will be provided in a newly-renovated laboratory with modern core facilities for molecular pathology and histology, imaging, genomics and proteomics, flow cytometry, analytical chemistry, nanotechnology, and access to Human Tissue Banks.

Interested candidates can apply on line at <https://secure.interfolio.com/apply/14217> and the following documents should be uploaded: curriculum vitae, names of five references (three for Assistant Professor applications), and a statement of research plans and career objectives. Review of applications will begin on **November 1, 2012** and will continue until the position is filled.

*Brown University is an Equal Opportunity (EEO/AA) Employer and is committed to increasing the diversity of its faculty. It welcomes nominations and applications from minorities, women, and individuals with varied experiences, perspectives and backgrounds, which would enrich the university's research, teaching and service missions.*



**OPEN FACULTY POSITIONS**  
 La Jolla, CA and Rockville, MD

**For nearly two decades our scientists have been at the forefront of the genomic revolution. Now, we want you to join us in our quest!**

J. Craig Venter Institute (JCVI) scientists have been unraveling and understanding the complexities of life as contained in the genomes of thousands of microbes, plants, and mammals, including humans. Our success is built on the philosophy of conducting science boldly in new interdisciplinary ways, using new tools and with the best scientists.

**JCVI is seeking qualified applicants for positions at all levels particularly in the following research focus areas:**

- Human and stem cell genomics
- Environmental genomics
- Human microbiome research
- Dynamics of host/pathogen interactions
- Synthetic biology
- Bioenergy
- Bioinformatics and computational biology
- Virology and vaccine development

Successful candidates will conduct innovative, independent research, collaborate with our interdisciplinary, highly collegial group of scientists within JCVI, and complement existing strengths within the Institute. Candidates must have a Ph.D. or M.D., a minimum of three years of Post-Doctoral research training, and be able to demonstrate the ability to establish and maintain a vigorous independent, externally funded research program. The level of appointment will be commensurate with experience.

JCVI offers an excellent working environment and a competitive benefits package. Interested applicants should apply directly in our career center by submitting their CV and a cover letter which includes a description of research interests and contact information for three references. JCVI's Career Center is located on our web site at [www.jcvi.org](http://www.jcvi.org).

Equal Opportunity Employer M/F/D/V



**Chemical Biology/Medicinal Chemistry**  
**Faculty Position**

The University of California, San Diego initiative in drug discovery invites applications from highly creative chemists for a tenure-track or tenured faculty position at the Assistant, Associate or full Professor level. The successful candidate will become part of the new Drug Discovery Institute, and will play a leading role in drug discovery efforts at UCSD by developing independent projects and cross-campus collaborations aimed at the identification, synthesis and optimization of new bioactive molecules, target validation, and assay development. He or she will also contribute to team-taught courses for Ph.D., Pharm.D., and M.D. students. The candidate should have a Ph.D. in chemical biology, synthetic organic chemistry, medicinal chemistry, or a closely related field.

UCSD offers a superb environment for interdisciplinary research, and many SSPPS faculty members hold joint appointments with other departments, such as Chemistry & Biochemistry and Pharmacology. The SSPPS has strong collaborations across the entire campus, including the Scripps Institution of Oceanography, Moores Comprehensive Cancer Center, and the Departments of Chemistry and Biochemistry, Pharmacology, Cellular and Molecular Medicine, and Medicine. Opportunities also abound for interactions with The Scripps Research Institute, Salk Institute, Sanford Burnham Institute, and La Jolla Institute of Allergy and Immunology, as well as hundreds of local pharmaceutical and biotechnology companies. State of the art facilities for chemical synthesis, high resolution NMR, mass spectrometry, and various spectroscopies, along with outstanding laboratory space, are available in the Pharmaceutical Sciences Building within the UCSD Health Sciences Center.

Candidates must have an outstanding record of scientific achievement, demonstrated by publications and patents. Strong independent grant funding and proven teaching experience are highly valued, and individuals with industrial experience are also encouraged to apply. Three letters of recommendation providing evaluations of the candidate's research caliber must be provided. Salary and appointment level will be commensurate with qualifications and experience and based on published UC pay scales for the Health Sciences. The successful candidate should be appointed by July 1, 2013; applications will be accepted until the position is filled.

Refer to job number **10-453** under the Faculty section at <http://pharmacy.ucsd.edu> for information. To apply, send a detailed resume/curriculum vitae and a statement of research interests and plans to: **Chair, Search Committee for Chemical Biology, c/o Cynthia Barlow, Human Resource Manager, Skaggs School of Pharmacy and Pharmaceutical Sciences MC 0657, University of California, San Diego, 9500 Gilman Drive, La Jolla, CA 92093-0657. E-mail: [ssppsapo@ucsd.edu](mailto:ssppsapo@ucsd.edu).**

**Please reference advertisement #SCIENCE2012JNRL.**

*UCSD is an Affirmative Action/Equal Opportunity Employer committed to excellence through diversity. Review of applications will begin September 1, 2012 and will continue until the position is filled.*



The Department of Physiology and Pharmacology at Des Moines University seeks to fill two open-rank, tenure-track faculty positions. The department aims to fill one position in the area of physiology and a second position in the area of pharmacology. Desirable applicants will either have preparation and expertise in physiology or pharmacology with an interest in teaching in the medical, podiatric, and health sciences curricula. Preference will be given to those candidates with demonstrated success in teaching a variety of physiology or pharmacology content areas. Applicants interested in the positions at the rank of Associate or Full Professor must have record of achievement in medical or health professions education, and a history of extramural funding. Des Moines University is committed to advancing its research enterprise and fostering an environment conducive to individual and collaborative scholarly success through the cultivation of distinctive faculty and student researchers who discover and disseminate new knowledge. Therefore, desirable applicants will be able to demonstrate the potential to develop an innovative and extramurally funded research program that will augment the department's current research strengths. Applicants must have an earned Ph.D. or equivalent and a minimum of two years postdoctoral experience.

For full consideration, candidates are invited to submit a letter of application stating their interest along with their curriculum vitae, a concise statement of teaching interests and educational philosophy, a well-defined research plan including specific aims and objectives and contact information for three references using the online applicant tracking system at [www.dmu.edu/employment](http://www.dmu.edu/employment). Review of applications will begin **October 1st, 2011** and continue until a successful candidate is identified and hired.

Candidates with questions specific to this position may contact the Search Committee Chair, **Dr. Matt Henry** at [Matthew.Henry@dmu.edu](mailto:Matthew.Henry@dmu.edu). For complete job description, Faculty benefit summary and/or information on Des Moines University, please visit [www.dmu.edu/employment](http://www.dmu.edu/employment).

*Des Moines University is an Equal Opportunity/Affirmative Action Employer. The University seeks excellence through diversity among its administrators, faculty, employees and students. The University prohibits discrimination on the basis of race, color, national origin, creed, religion, age, disability, sex, gender identity, sexual orientation, veteran status, genetic information or any other legally protected status. Applications by members of all underrepresented groups are encouraged.*



**Two Faculty Positions:**  
**Genome Architecture/Function**  
**Molecular Cell Biology**  
Biochemistry and Molecular Biology Department  
Colorado State University



The Department of Biochemistry and Molecular Biology seeks applicants for two tenure-track positions at the Assistant or Associate Professor level. For the position in Genome Architecture/Function, we encourage individuals with a strong background in studying DNA-related processes in eukaryotes (e.g. transcription, DNA repair and replication, cell division, genomics or epigenetics) to apply. For the position in Molecular Cell Biology, we are seeking candidates with an interest in studying molecular mechanisms of eukaryotic cellular processes and cell architecture (e.g. regulation of the cytoskeleton, cell cycle control, protein trafficking and folding, and cell motility). The Department has outstanding research programs in the areas of cell, molecular, and structural biology, with a strong core group studying the molecular mechanisms of cellular functions ranging from transcription to cell division. The two positions are part of a strategic plan designed to further strengthen and expand these areas of excellence and, therefore, candidates are expected to complement the current strengths in our department. Required credentials include a doctoral degree, post-doctoral experience, and evidence of expertise in the broad areas defined above. Candidates applying for appointment as an Associate Professor must have an internationally recognized and well-funded research program.

Applicants should submit their application on-line, and upload their curriculum vitae, statements of research and teaching interests at: <http://cns.natsci.colostate.edu/employment/BMB/>. Applicants at the Assistant level should request three reference letters. Referees will be sent an access code (using the contact information provided by the applicant) for submitting the letters online. Applicants at the Associate level will be asked to supply reference letters should they be selected as a semi-finalist. The co-chairs of the search committee are **Dr. Karolin Luger** and **Dr. Jennifer DeLuca**. For full consideration, complete applications should be received by **November 1, 2012**. However, applications may be considered until the positions are filled. Complete applications of the semi-finalist candidates will be available to department faculty for review.

*Colorado State University is an EO/EA/AA Employer. Colorado State University conducts background checks on the final candidates.*



**Memorial Sloan-Kettering  
Cancer Center**

*The Best Cancer Care. Anywhere.*

**FACULTY POSITION**  
**Cell Biology Program**

The Cell Biology Program, Sloan-Kettering Institute ([www.ski.edu](http://www.ski.edu)) has initiated a search for tenure-track faculty members. We are interested in outstanding individuals who have the potential to develop an innovative, independent research program that complements and enhances our existing strengths.

Candidates with research interests in exciting areas of eukaryotic cell biology, including aspects of stem cell biology, and using a variety of experimental approaches and systems are encouraged to apply.

New faculty will be eligible to hold graduate school appointments in the Gerstner Sloan-Kettering Graduate School of Biomedical Sciences, the Weill Cornell Graduate School of Medical Sciences of Cornell University, as well as the Tri-Institutional MD/PhD Training Program. Sloan-Kettering has an outstanding infrastructure as well as state-of-the-art core facilities resources, and we are expanding our research programs.

The deadline for applications is **November 1, 2012**. Interested candidates should visit <http://facultysearch.ski.edu> to access the on-line faculty application. Please visit the site as soon as possible, as it contains important information regarding the required application materials, including deadlines for submission of letters of reference. Informal inquiries may be sent to **Tiffany Lennon** at [lennont@mskcc.org](mailto:lennont@mskcc.org) or **Dr. Alan Hall**, Chair, Cell Biology Program at [halla@mskcc.org](mailto:halla@mskcc.org).

**facultysearch.ski.edu**

MSKCC is an equal opportunity and affirmative action employer committed to diversity and inclusion in all aspects of recruiting and employment. All qualified individuals are encouraged to apply.



**Memorial Sloan-Kettering  
Cancer Center**

*The Best Cancer Care. Anywhere.*

**TENURE TRACK FACULTY POSITION**  
**Cancer Pharmacology or Drug Discovery**

Sloan-Kettering Institute is seeking an innovative individual who wishes to address problems of relevance to cancer drug discovery and development for a tenure-track position at the Assistant or Associate Member level with strong research accomplishments in biology, biochemistry or pharmacology. Faculty will be eligible to hold graduate school appointments in the Gerstner Sloan-Kettering Graduate School of Biomedical Sciences, the Weill Graduate School of Medical Sciences of Cornell University, as well as the Tri-Institutional MD/PhD Training Program and Tri-Institutional Training Program in Chemical Biology.

MSKCC offers a unique and exciting research environment with programs in Immunology, Pharmacology, Chemistry, Molecular Biology, Computational Biology, Genetics, Cell Biology, Developmental Biology, Cellular Biochemistry and Structural Biology. The presence of world-renowned clinical programs in cancer research, treatment and prevention offers unique opportunities for creative collaboration.

Applicants should have a PhD and/or MD degree, postdoctoral experience, and dedication to important problems at the interface of biology, biochemistry or chemistry as they relate to cancer pharmacology.

The deadline for applications is **November 1, 2012**. Interested candidates should visit <http://facultysearch.ski.edu> to access the on-line faculty application. Please visit the site as soon as possible, as it contains important information on the required application materials, including deadlines for submission of letters of reference. Inquiries may be sent to **Marie Aiello** at [aiellom@mskcc.org](mailto:aiellom@mskcc.org) or to **Dr. David Scheinberg**, Chairman, Molecular Pharmacology and Chemistry Program at [scheinbd@mskcc.org](mailto:scheinbd@mskcc.org).

**facultysearch.ski.edu**

MSKCC is an equal opportunity and affirmative action employer committed to diversity and inclusion in all aspects of recruiting and employment. All qualified individuals are encouraged to apply.

# The best ideas in medicine start with the best people.

At Stony Brook Medicine, our highest calling is to put the power of ideas to work in our patients' lives. Stony Brook Medicine integrates and elevates all of Stony Brook University's health-related initiatives: education, research and patient care. It includes Stony Brook University Hospital, Long Island's premier academic medical center. With 597 beds, SBUH is the region's only tertiary care center and Regional Trauma Center. We are home of the Stony Brook Heart Institute, Stony Brook Cancer Center, Stony Brook Long Island Children's Hospital, Stony Brook Neurosciences Institute and Stony Brook Digestive Disorders Institute. At Stony Brook Medicine, we put the power of ideas to work. Join our team at Stony Brook Medicine – the best ideas in medicine.

## Deputy Director of Clinical Affairs

The Stony Brook University Cancer Center is seeking candidates and nominees for the Deputy Director for Clinical Affairs. The candidate will provide leadership in the Cancer Center's clinical affairs, clinical research activities and training. The Deputy Director for Clinical Affairs will have the opportunity to oversee the recruitment of up to ten new faculty positions with expertise in clinical or translational cancer research, working with the Director and Chairpersons of key departments.

The successful candidate will help formulate and execute the Cancer Center's clinical strategic plan and be actively engaged in the oversight and quality management of multidisciplinary cancer care. The Deputy Director for Clinical Affairs position entails working closely with the Director to further advance clinical research, including clinical trials programs, with the ultimate goal of becoming an NCI-designated cancer center. The Deputy Director will work closely with internal and external advisory boards, and with the Advancement Office. The selected candidate will hold a faculty appointment in the appropriate School of Medicine academic department. With the recent approval of the NYSUNY 2020 Challenge Grant to the University and the announcement of the largest gift ever to public higher education in the State of New York, Stony Brook Medical School is embarking on a transformational expansion of the biomedical and clinical research enterprise. The investment in cancer research will include major program development, including the development of new programs and the construction of a new state-of-the-art 250,000 sq. ft. research and clinical cancer center.

Applicants for this position should have a record of extramural funding and accomplishments in clinical and/or translational research, as well as experience in developing complex integrative programs. Candidates should demonstrate the highest level of ethical conduct and a commitment to diversity. Required Academic and Professional Credentials: The successful candidate will have an MD degree and demonstrated administrative leadership and clinical research experience. Must be eligible for a tenured faculty appointment in accordance with the criteria established by the School of Medicine (School of Medicine's Criteria for Appointment, Promotion and Tenure). Review of applications will continue until the position is filled.

For a full position description, application procedures or to apply online, visit [www.stonybrook.edu/jobs](http://www.stonybrook.edu/jobs) (Ref. #: F-7431-12-08). Nominations and applications, including a State employment application and curriculum vitae, should be submitted to:

Theodore G. Gabig, MD, Professor and Chief  
Division of Medical Hematology/Oncology Search Committee Chair  
c/o: Ms. Lauren Cutaia, Health Sciences Tower L-4, Room 178, Stony Brook, NY 11794-8430

Stony Brook University/SUNY is an affirmative action, equal opportunity educator and employer.



Stony Brook  
Medicine

## UNIVERSITY OF LOUISVILLE The Center for Oral Health and Systemic Disease

### University of Louisville Faculty Positions

The Center for Oral Health and Systemic Disease (<http://louisville.edu/dental/oralhealth>), housed in the School of Dentistry at the University of Louisville, invites applications for two full time tenure/tenure track positions at the level of Assistant, Associate or Full Professor. The Center comprises investigators focused on microbial pathogenicity, innate immunity and inflammation, and we are looking for applicants interested in fundamental disease mechanisms and host responses. Applicants should possess the Ph.D., D.D.S./D.M.D. or equivalent degree. At the Assistant Professor level a minimum of 3 years postdoctoral experience is required. The successful applicant will demonstrate creativity and research excellence, and be expected to develop a strong independent research program. At the Associate or Full Professor level the successful candidate will have an outstanding record of innovative, well-funded research and will be expected to maintain a strong extramurally funded research program. Competitive startup packages along with opportunities for cross appointments in a basic science department in the School of Medicine are available.

Applications should be made online (<http://louisville.edu/hr/employment/current-openings>) and include a curriculum vitae, a statement of research interests and goals, and contact information for three referees. Informal inquiries can be directed to Richard J. Lamont, Ph.D., Director, Center for Oral Health and Systemic Disease, [rich.lamont@louisville.edu](mailto:rich.lamont@louisville.edu). Completed applications will be reviewed on a rolling basis until the positions are filled.

*The University of Louisville is an Affirmative Action, Equal Opportunity, Americans with Disabilities Employer, committed to diversity and in that spirit, seeks applications from a broad variety of candidates.*

## BOSTON UNIVERSITY

### Bioinformatics Graduate Program Faculty Position

The Bioinformatics Graduate Program at Boston University invites applications from energetic and promising teacher-scientists for a tenure-track assistant professorship. The Program, centered in the interdisciplinary Life Science and Engineering Building in the heart of Boston, is University-wide and includes some 50 faculty from the Colleges of Engineering, Arts and Sciences, components of the Medical campus including the National Emerging Infectious Disease Laboratory (NEIDL), and adjunct faculty from major biotechnology companies, the Broad Institute, Harvard Medical School, and the National Institutes of Health. Graduate students are drawn from diverse disciplines, and selection is extremely competitive. More than 60 PhD students are currently pursuing leading edge research in areas ranging from whole-genome analysis, structural genomics, and systems biology, to clinical applications (<http://www.bu.edu/bioinformatics/>).

The successful candidate will have concrete plans for establishing a world-class computational research program in one of the following areas: evolutionary biology, population genetics, systems biology, proteomics or comparative genomics. Exceptionally strong candidates in other areas may also be considered. Candidates must have a strong biological and computational background, with primary training in either mathematical statistics, chemistry, physics, computer science or a life science.

Review of applications will begin on **30 November 2012** and continue until the position is filled. Applicants must apply through AcademicJobsOnline.org, job reference number **1875**, by submitting a CV, a complete bibliography, a research plan, a statement of teaching interests, and at least three letters of recommendation.

*Boston University is an Equal Opportunity/Affirmative Action Employer.*





## PRINCETON UNIVERSITY

### ASSISTANT PROFESSORSHIP MOLECULAR EVOLUTION

Princeton University's Departments of Ecology and Evolutionary Biology and of Molecular Biology jointly plan to hire one individual at the level of tenure-track Assistant Professor, with a focus on molecular evolution. We seek an individual who would have strong connections in both departments. Sample areas might include, but are not limited to, microbial evolution, experimental evolution, epigenetics, metagenomics, and/or the evolution of development, using traditional and/or emerging model systems. We seek applicants who pursue experimental research that aims for significant conceptual and empirical integration across traditional disciplinary boundaries and who have a strong commitment to teaching.

Applicants should write a vision statement, no longer than 2 pages, that outlines one or more major unsolved problems in their field and how they plan to address them. The vision statement must be more than a précis of the applicant's prior and current research. Applications, including the vision statement, curriculum vitae, three reprints and contact information for three references, can be submitted online via <http://jobs.princeton.edu>, requisition #1200524. Screening of applications will begin 1 October, 2012.

*Princeton University is an Equal Opportunity Employer and complies with applicable EEO and Affirmative Action regulations.*

### Neurobiology of Disease Faculty Position



### Gladstone Institutes and the University of California, San Francisco

The Gladstone Institute of Neurological Disease and the University of California, San Francisco (UCSF) invite applications for a faculty position at the level of Assistant, Associate, or full Professor. Primary criteria for appointment will be outstanding records of innovative research and academic performance, including landmark papers in leading journals, as well as proven abilities or high potential to establish a rigorous and substantial independent research program, provide exemplary mentorship, and engage in fruitful collaborations.

The successful candidate will join an interactive group of investigators in Gladstone's state-of-the-art research facility at UCSF's Mission Bay campus. S/he will have joint appointments in the Gladstone Institute of Neurological Disease and in the Neuroscience Graduate Program and the Biomedical Sciences Graduate Program at UCSF. Excellent salary support is provided. Women and underrepresented minorities are especially encouraged to apply. The search will continue until the position is filled. However, to ensure full consideration, applications should be received by **November 1, 2012**.

Please send curriculum vitae, description of achievements and research interests, and the names of three references to:

**GIND/UCSF Search Committee**  
1650 Owens Street  
San Francisco, CA 94158  
[gindsearch@gladstone.ucsf.edu](mailto:gindsearch@gladstone.ucsf.edu)

## GLADSTONE

The Gladstone Institutes and UCSF are Affirmative Action/Equal Opportunity Employers. They undertake affirmative action to assure equal employment opportunity for underutilized minorities and women, for persons with disabilities, and for Vietnam-era veterans and special disabled veterans.



## STANFORD SCHOOL OF MEDICINE

Stanford University Medical Center

### FACULTY POSITION Department of Biochemistry

Applications or nominations are invited for an Assistant Professor position in the Department of Biochemistry. We are seeking individuals with an extraordinary record of scientific accomplishment and creativity working in any area of biochemistry, biophysics or molecular biology research, broadly defined. As a basic science department within the School of Medicine, we encourage applications focused on the molecular basis of human health and disease as well as those focused on fundamental mechanisms of life. The principal criterion for appointment in the University Tenure Line is a major commitment to research and teaching.

Candidates should submit in **one complete PDF document**: a curriculum vitae including a list of publications, a description of research accomplishments and future plans, and contact information for three references to [Biochemistry\\_Recruitment@stanford.edu](mailto:Biochemistry_Recruitment@stanford.edu). Applications should be received by **December 7, 2012**. References should send their letters electronically to the above email address or hardcopy to: **Search Committee Chair, Department of Biochemistry, Stanford University School of Medicine, 279 Campus Drive, Room B400, Stanford, CA 94305-5307.**

*Stanford University is an Equal Opportunity Employer and is committed to increasing the diversity of its faculty. It welcomes nominations of and applications from women and members of minority groups, as well as others who would bring additional dimensions to the University's research, teaching and clinical missions.*



### UNIVERSITY OF MICHIGAN FACULTY POSITIONS IN MOLECULAR, CELLULAR, AND DEVELOPMENTAL BIOLOGY

The Department of Molecular, Cellular, and Developmental Biology in the College of Literature, Science and the Arts at the University of Michigan solicits applications for faculty positions at the assistant professor level, but appointment at a more senior level is possible for applicants with suitable experience. The faculty position will be tenured or tenure track with a university year appointment starting September 1, 2013 or January 1, 2014. Successful candidates will be expected to establish a vigorous, extramurally funded research program and to be involved in instruction of both undergraduate and graduate students.

We welcome applications from outstanding biologists in any area of research within the scope of the department, which includes genetic, physiological, and biochemical studies of model organisms (plants, animals, and microbes). We particularly encourage applicants studying genomics/biological networks, molecular/cellular neuroscience, plant molecular biology, or structural biology. For further information about research areas in the department, please visit [www.mcdb.lsa.umich.edu](http://www.mcdb.lsa.umich.edu).

All applications must be submitted on-line at <http://www.mcdb.lsa.umich.edu/recruitment>. You will be asked to upload the following materials: A cover letter, a *curriculum vitae*, a brief summary of recent research accomplishments and statement of future research plans, a statement of teaching interests and philosophy, and evidence of teaching excellence for those who have teaching experience. Candidates for appointment as an assistant professor should provide names and contact information for at least three references, as instructed in the on-line application form. To ensure full consideration, all materials should be received by **October 8, 2012**.

*Women and underrepresented minorities are encouraged to apply. The University of Michigan is supportive of the needs of dual career couples and is an Equal Opportunity/Affirmative Action Employer.*

The Department of Biology at Johns Hopkins is seeking to hire several talented new faculty members at the junior and senior levels. This is part of a major, multi-year expansion of the Department, including the addition of new faculty, infrastructure and research space. Successful candidates will have the opportunity to have a strong impact on their environment, forge strong connections with scientists throughout the Johns Hopkins community and influence the future direction of Biomedical research at Hopkins. More information about the Department can be found at <http://www.bio.jhu.edu>. Applications from women and minority candidates are especially encouraged. Johns Hopkins University is an Equal Opportunity/Affirmative Action Employer.

### TENURED FACULTY POSITIONS FOR DISTINGUISHED FACULTY

We invite applications from mid-career faculty at the level of Associate or Full Professor with Tenure. Candidates should be distinguished in their field of study with a strong track record of productivity and funding. Candidates in any area of Biology will be considered, but those that complement the department's current strengths, bridge traditional disciplinary boundaries and can form collaborations between departments are particularly attractive. Please submit your *confidential* application files, including a CV, statement of current and future research, and statement of teaching interests and philosophy to: <http://www.interfolio.com/apply/14654>. We will begin reviewing applications on **October 15, 2012**; the search will remain open until all positions are filled.

### TENURE-TRACK FACULTY POSITIONS IN FUNCTIONAL GENOMICS

We invite applicants who apply genomic, bioinformatic and quantitative approaches to investigate biological problems in creative and innovative ways. Candidates that bridge traditional disciplinary boundaries will be particularly attractive. Successful candidates will be expected to establish a vibrant research program and to participate in undergraduate and graduate teaching. Please submit your application files including a CV, statement of current and future research, and statement of teaching interests and philosophy, and arrange to have three confidential letters of recommendation submitted through: <http://www.interfolio.com/apply/14207>. The deadline for receipt of all materials is **November 1, 2012**.

### TENURE-TRACK FACULTY POSITIONS IN BIOLOGY

Candidates in any area of Biology will be considered, but areas we have specifically targeted for growth include: organization and regulation of the genome, metabolite regulation of cellular processes and physiology, microbiology and host-microbe interaction, stem cell biology and regeneration. Candidates that bridge traditional disciplinary boundaries will be particularly attractive. Successful candidates will be expected to establish a vibrant research program and to participate in undergraduate and graduate teaching. Please submit your application files including a CV, statement of current and future research, and statement of teaching interests and philosophy, and arrange to have three confidential letters of recommendation submitted through: <http://www.interfolio.com/apply/14207>. The deadline for receipt of all materials is **November 1, 2012**.



### Facility Position in Stem Cell Biology

The Children's Research Institute (CRI) at the University of Texas-Southwestern Medical Center in Dallas, TX seeks applications for a **tenure-track faculty position in the area of stem cell biology**. Outstanding investigators at any rank will be considered. Candidates must have a Ph.D., M.D. or equivalent degrees and the ability to direct an independently-funded research program exploring any aspect of stem cell biology.

The UT-Southwestern Medical Center has a long and distinguished history of excellence in disease-related basic science research. The CRI is a new institute recruiting outstanding individuals dedicated to solving fundamental problems in biology and disease. The CRI is a dynamic, stimulating, and highly collaborative scientific environment. Major areas of focus within the CRI will include stem cell biology, cancer biology, and metabolism.

Please submit a CV, a 2-page summary of past accomplishments and research plans, and ask three references to submit letters by **November 1, 2012** to [CRIApplicants@utsouthwestern.edu](mailto:CRIApplicants@utsouthwestern.edu).

*UT Southwestern is an Equal Opportunity/Affirmative Action Employer.*

## UC DAVIS

### Assistant Restoration Ecology Specialist in Cooperative Extension Department of Plant Sciences

Assistant Specialist in Cooperative Extension. An 11-month, career-track extension position with 100% Cooperative Extension responsibilities located in the UC Davis Department of Plant Sciences. Candidate will provide statewide research and extension leadership in restoration and conservation of multiple goals in working landscapes, including a focus on both natural (e.g., grasslands, wetlands, woodlands) and managed (e.g., rangeland, agricultural, urban, parks) ecosystems, and their interactions. Focal goals include, but are not limited to: safe and sustainable forage and food production; conservation and restoration of diverse species; enhanced provisioning of fertile soil, pollination, clean air; and control over pests and erosion. This CE Specialist will bring statewide leadership, visibility, and cohesion to an interdisciplinary team of land grant researchers and educators to improve the success of ecosystem restoration projects. This position will support the ANR Rangeland Watershed Workgroup that coordinates the natural resources research and education activities of more than 40 CE advisors, CE specialists and AES researchers. Research will be conducted in the laboratories and fields at UC Davis, on diverse stakeholder lands (e.g. nature reserves, local, state and federal lands, and commercial farms and ranches), and at UC Field Stations located throughout California. Specific research could include improving land management practices, developing site specific restoration and invasive species control guidelines and monitoring restoration progress in an effort to provide diverse plant communities/habitats and stable watersheds that ensure sustainable forage production, provide safe supplies of water, resist pest invasions, aid beneficial insects and support safe sustainable food systems. The candidate is expected to develop a nationally-recognized program, secure extramural funding, and publish research results in appropriate refereed journals and reports. Candidate will interact with diverse clientele groups, provide farm advisor training and advising, and develop an affirmative action program. Candidate will have the opportunity to participate in departmental teaching and in directing undergraduate and graduate research. Requirements include: a Ph.D. in restoration ecology, ecosystem management, rangeland ecology, plant ecology, plant biology, plant science, weed science, soil ecology, or a closely related field; leadership ability, management and communication skills; ability to conduct independent research must be demonstrated.

Candidates should begin the application process by registering online at <http://recruitments.plantsciences.ucdavis.edu/>. Please include statements of research and extension interests, *curriculum vitae*, publication list, copies of 3 of your most important research publications, copies of undergraduate and graduate transcripts (if within 5 years of either degree), and the names, e-mail addresses, and telephone numbers of at least five professional references. For administrative questions regarding the application process, please email Ms. Baljit Nijjar, [bknijjar@ucdavis.edu](mailto:bknijjar@ucdavis.edu). Review of the applications for this position will begin **November 1, 2012**. The position will remain open until filled.

*UC Davis is an Affirmative Action/Equal Employment Opportunity Employer and is dedicated to recruiting a diverse faculty community. We welcome all qualified applicants to apply, including women, minorities, veterans, and individuals with disabilities.*

## POSITIONS OPEN



### ASSISTANT PROFESSOR

The Department of Biological Chemistry at the University of Michigan (UM) invites applications from outstanding junior investigators for a tenure-track position as an Assistant Professor. The Department seeks candidates whose research encompasses biochemical approaches to broad areas of molecular, cellular, neuro- and developmental biology and metabolism. Ideally, the research program of the successful applicant will complement existing strengths in structural enzymology, protein folding and processing, biochemical signaling, and regulation of gene expression. Qualifications include a Ph.D. and/or M.D. and a minimum of two years of postdoctoral research. The successful candidate will develop an active biochemical research program, train predoctoral students and postdoctoral fellows, and participate in the departmental teaching and service activities.

The Department of Biological Chemistry is a highly collaborative and cooperative environment, providing many opportunities for scientific interactions within the department, the Medical School, and across the UM campus. For further information on the current 45 active tenured and tenure-track faculty (including joint appointees), see **website: <http://www.biochem.med.umich.edu/>**.

Applications should be assembled into a single PDF file and include a cover letter, a NIH Biosketch, curriculum vitae, and a brief Research Plan (three pages). All materials should be sent to the Junior Faculty Search Committee electronically, care of **Amanda Howard (e-mail: [amanhowa@umich.edu](mailto:amanhowa@umich.edu))**. Three letters of reference should also be sent directly to the Search Committee electronically (e-mail: [amanhowa@umich.edu](mailto:amanhowa@umich.edu)). Alternatively, letters can be sent as hard copies to: **Junior Faculty Search, Department of Biological Chemistry, 5301 MSRBIII, 1150 West Medical Center Drive, University of Michigan Medical School, Ann Arbor, MI 48109-0606**. Applications will be reviewed beginning October 15, 2012 and continue until the position is filled. Initial interview offers will be made by December 15.

*The University of Michigan is an Affirmative Action/Equal Opportunity Employer.*

### YALE UNIVERSITY Energy Sciences Institute

Yale University seeks to recruit faculty at the **ASSISTANT PROFESSOR** level to the newly established Energy Sciences Institute. The Institute is one of several science and engineering initiatives located at Yale's West Campus, a recently acquired 137-acre campus that has provided the University with unparalleled opportunities to stimulate and support cutting-edge, interdisciplinary research. We seek creative teacher-scholars who will have primary appointments in either the Chemistry Department or the School of Engineering and Applied Science. Candidates must have a Ph.D. in a relevant discipline, and an outstanding record of research that demonstrates originality in addressing significant questions in the study of energy. The Search Committee is particularly interested in individuals with expertise and research interests in the conversion of solar energy into storable chemical energy as well as those with interest in the development of "transitional technologies," such as clean fuels and carbon capture and sequestration. Applicants should create a profile at **website: <https://academicjobsonline.org/ajo/jobs/1722>** and upload a statement of research plans, curriculum vitae, and up to five reprints of published work(s). Applicants should also arrange for three references to upload their letters of recommendation. For further information, contact: **Ryan Nystrom** at e-mail: [ryan.nystrom@yale.edu](mailto:ryan.nystrom@yale.edu) or P.O. Box 27394 West Haven, CT 06516-7390. The review of applications will begin on October 15, 2012. *Yale University is an Affirmative Action/Equal Opportunity Employer. Yale values diversity among its faculty, students, and staff and strongly encourages applications from women and under-represented minorities.*

## POSITIONS OPEN



### UNIVERSITY OF PENNSYLVANIA

The School of Arts and Sciences at the University of Pennsylvania invites applications for a tenure-track **ASSISTANT PROFESSOR** appointment in evolution, broadly interpreted. We are interested in exceptional scientists and mathematicians who have well-developed research programs employing mathematical or computational techniques to study the evolution of dynamical processes far from equilibrium in the context of any of the following: biology, chemistry, or materials from the molecular to the systems scale, language, geology, psychology, or the environment. The successful candidate's primary appointment will be in a single department in the natural sciences: Biology, Chemistry, Earth and Environmental Science, Linguistics, Mathematics, Physics and Astronomy, or Psychology. Secondary appointments in other departments can be arranged, as appropriate. This appointment will be the first in a cluster of appointments across the natural sciences in various aspects of evolution; the successful candidate should therefore have a strong interest in building such a program and in interacting with researchers from other disciplines whose research lies within the overarching theme of evolution. The successful candidate will teach courses in his or her home department and will participate in the development of curriculum pertinent to the theme of the cluster.

Applications should be submitted online at **website: [facultysearches.provost.upenn.edu/applicants/Central?quickFind=51089](http://facultysearches.provost.upenn.edu/applicants/Central?quickFind=51089)** and include curriculum vitae, a research statement that includes the candidate's perspective on how she or he fits into one of the core departments, links to no more than three journal publications, and the contact information for three individuals who will be contacted by the University with instructions on how to submit a letter of recommendation. Review of applications will begin 16 November 2012 and will continue until the position is filled. *The University of Pennsylvania is an Affirmative Action/Equal Opportunity Employer and is strongly committed to establishing a diverse faculty; website: <http://www.upenn.edu/almanac/volumes/v58/n02/diversityplan.html>.*

### TENURE-TRACK ASSISTANT PROFESSOR Biophysics University of Michigan

Biophysics at the University of Michigan anticipates that at least one tenure-track faculty position will be available with a September 2013 starting date. The position is an Assistant Professorship with a university year appointment. Appointment at a higher rank may be considered for candidates with an exceptional record of productivity. We are considering applications in all areas of biophysics, especially those areas focused on problems of biological significance that use and develop modern biophysical methodologies. We are primarily interested in quantitative experimental or theoretical work across the molecular and cellular scales, including biological networks. Information about our research areas can be found at **website: <http://www.umich.edu/~biophys/>**. Candidates are required to have a doctoral degree in biophysics or a related field such as chemistry, biological chemistry, physics, etc. The successful candidate is expected to establish an independent research program and to contribute effectively to the Department's undergraduate and graduate teaching programs. Applicants should submit curriculum vitae, a brief statement of present and future research plans, a statement of teaching philosophy and experience, at least three letters of recommendation, and evidence of teaching experience, if any. The deadline for applications is October 14, 2012. Applications can be submitted to **website: <http://www.umich.edu/~biophys/>**. If you should have any questions, please feel free to contact **Ann Titus** at e-mail: [atitus@umich.edu](mailto:atitus@umich.edu) or telephone: 734-764-1146. *Women and minorities are encouraged to apply. The University of Michigan is supportive of the needs of dual career couples and is an Equal Opportunity/Affirmative Action Employer.*

## POSITIONS OPEN



### ASSISTANT PROFESSOR of Infectious Disease Ecology/Evolution

The School of Biological Sciences at Illinois State University in Normal, IL (**website: <http://www.bio.illinoisstate.edu>**) invites applications for a tenure-track position as Assistant Professor in the area of Ecology/Evolution of Infectious Disease. The successful applicant should be engaged in research investigating principles of transmission dynamics of infectious disease in natural systems, including ecological or evolutionary processes and impacts. Requirements include a Ph.D., or equivalent, postdoctoral research experience, potential to secure external funding, and an interest in working within a diverse intellectual community. We seek a colleague with the potential to develop collaborations with current faculty investigating vector ecology, immunology, biomathematics, conservation, or microbiology. The successful applicant will be expected to develop an independent externally funded research program, to mentor graduate and undergraduate research students, and to teach graduate and undergraduate courses. Salary is commensurate with qualifications and experience. The School of Biological Sciences at Illinois State University is home to about 60 M.S. and Ph.D. students and over 500 undergraduate majors. To apply, send: a descriptive cover letter, curriculum vitae, a one- to two-page statement of future research goals, and contact information for three references (as a single PDF); and up to three representative reprints (as separate PDFs) to **Dr. Steven Juliano, c/o Sally Little via e-mail: [salitt2@ilstu.edu](mailto:salitt2@ilstu.edu)**. Review of applications will begin on November 1, 2012 and continue until the position is filled. Intended start date: August 16, 2013.

*Illinois State University is an Equal Opportunity University encouraging diversity.*

### ASSISTANT PROFESSOR Plant Physiology/Plant Development

The Department of Biology at the College of William & Mary seeks applications for a tenure-track position at the Assistant Professor level in Plant Physiology or Plant Development to begin August 10, 2013. The successful candidate will be expected to maintain an extramurally funded research program involving both undergraduate and Master's degree students. Teaching responsibilities are a plant physiology course with laboratory, the lecture portion of a large course in integrative general botany to be taught in alternate years, and another course in the area of the candidate's expertise to alternate with general botany. Candidates must demonstrate the potential and motivation to achieve excellence in teaching. This includes communication skills and the ability to engage highly motivated students in both large and small courses, from molecular to whole-organism levels of biological organization. Applicants must hold a Ph.D. with a focus in plant science at the time of application, and postdoctoral research experience is expected. Previous experience teaching undergraduate courses and mentoring research students would be viewed favorably. Candidates must apply online at **website: <https://jobs.wm.edu>**. Submit a cover letter, curriculum vitae, statements of research plans and teaching philosophy, and a list of courses relevant to the botanical sciences taken and taught. You will be prompted to submit online the names and e-mail addresses of three references who will be contacted by us with instructions for how to submit a letter of reference. For full consideration, submit application materials by the review date, November 1, 2012. Applications received after the review date will be considered if needed. For questions about the position, contact **Dr. Martha Case (e-mail: [macase@wm.edu](mailto:macase@wm.edu))**. More information about the College of William & Mary can be found at **website: <http://www.wm.edu>**. *The College of William & Mary conducts background checks on applicants for employment. The College is an Equal Opportunity/Affirmative Action Employer.*





### Cell Biology Faculty Positions

The Department of Cell Biology at the University of Pittsburgh, School of Medicine seeks candidates for Assistant, Associate and/or Full Professor tenure stream and tenured faculty positions. We encourage applications from candidates with a strong record of research accomplishments in the broad area of cell biology, including, but not limited to intracellular signaling, membrane trafficking, organelle dynamics and biogenesis, cytoskeleton, autophagy and systems biology aimed at basic cell biology questions. The successful candidate will join an interactive, interdisciplinary group of faculty, students and fellows, and enjoy access to the state-of-the-art equipment and facilities at the University of Pittsburgh. Candidates must hold a Ph.D. or an equivalent degree. Highly competitive start-up, compensation and benefits packages are offered.

Curriculum vitae, statement of research interests, two recent most important papers, and e-mail addresses of three references can be sent to: [cbprecr@pitt.edu](mailto:cbprecr@pitt.edu). Review of applications will begin immediately and continue until the position is filled.

*The University of Pittsburgh is an Equal Opportunity/Affirmative Action Employer.*



### Faculty Position in Developmental Neuroscience at Arizona State University

The School of Life Sciences at Arizona State University invites applications for an Assistant tenure track faculty position from individuals working on cutting edge issues in developmental neuroscience. Candidates performing research in the following areas are preferred:

- 1) Molecular and genetic approaches to examine mechanisms regulating embryonic or postembryonic neural development, stem cells and neural plasticity.
- 2) Functional genomic and/or epigenetic approaches to elucidate complex phenotypes in neurobiology, including development, regeneration, neurodegenerative diseases, and behavior.

The successful candidate will be expected to develop an innovative, extramurally funded, research program, teach at the undergraduate and graduate levels, and have a commitment to outreach and service. The successful candidate will be expected to mentor undergraduate and graduate students as well as postdoctoral fellows. More information on neuroscience graduate education at ASU can be found at <http://neuroscience.asu.edu>. A competitive startup package and teaching load compatible with high research productivity will be provided. Arizona State University has made a commitment to accelerating the translation of basic discoveries into practical benefits for society through the construction of state-of-the-art research facilities and the recruitment of world-class faculty members. Faculty in this position will join a growing neurobiology research cluster in the School of Life Sciences, Department of Psychology, School of Biological and Health Systems Engineering, and the Biodesign Institute. Key collaborative opportunities exist with a wide range of partner institutions in the Phoenix metropolitan area, such as the Mayo Clinic, Phoenix Children's Hospital, the Translational Genomics Research Institute, the Barrow Neurological Institute, and the Banner Alzheimer's Institute.

Candidates must have a Ph.D. (or equivalent) in an appropriate field, and a minimum of 2 years of postdoctoral training is preferred. Demonstrated teaching and research excellence is preferred.

To apply, send a cover letter, your curriculum vitae, three representative publications, separate statements of future research plans and teaching philosophy and interests, and contact information for three references to be sent to **Kenro Kusumi, Chair, Developmental Neuroscience Faculty Search Committee, School of Life Sciences, PO Box 874501, Tempe, AZ 85287-4501**. Electronic applications sent as PDF files to [solsfacultysearch2@asu.edu](mailto:solsfacultysearch2@asu.edu) are preferred. The initial closing date for receipt of applications is **October 14, 2012**; applications will be reviewed weekly thereafter until the search is closed. For additional information on the School of Life Sciences, please visit <http://sols.asu.edu>.

*A background check is required for employment. Arizona State University is an Equal Opportunity/Affirmative Action Employer committed to excellence through diversity. We especially encourage women and minorities to apply.*



### Faculty Positions Department of Neuroscience

Scripps Florida is seeking outstanding applicants for tenured faculty positions at advanced levels (Associate Professor or Professor) in the Department of Neuroscience at its newly opened, state-of-the-art campus in Jupiter, Florida. The Jupiter campus of the Scripps Research Institute offers a rapidly growing, dynamic environment and is committed to provide a multi-disciplinary, collaborative atmosphere for fostering cutting edge neuroscience research. We invite applications from ambitious and interactive investigators applying integrative molecular, genetic, biochemical, biophysical, cellular (iPSC), anatomical, and behavioral approaches to elucidate the mechanisms underlying nervous system function. In addition to basic neuroscience, we have a keen interest in human neuropsychiatric disorders, animal models for these disorders, and CNS drug discovery. The state-of-the-art facilities at Scripps Florida house expertise in proteomics, crystallography, pharmacokinetics, medicinal chemistry, rodent behavior, and ultra high-throughput small molecule screening for drug discovery.

Scripps Florida offers exceptional startup packages and an outstanding intellectual environment for fostering top-tier basic and translational research. Further information about our expanding Department of Neuroscience can be found at <http://www.scripps.edu/florida/neuro/>. Interested candidates should submit their *Curriculum Vitae* and contact information for at least three professional references as a single PDF file, to:

**Dr. Ronald L. Davis, Chairman, Department of Neuroscience**  
c/o Trina Kemp  
([trmiles@scripps.edu](mailto:trmiles@scripps.edu))

**The Scripps Research Institute, Scripps Florida**  
130 Scripps Way  
Jupiter, Florida, 33458

*TSRI embraces diversity and recognizes it as being a key to our success.  
EOE/M/F/V/D.*



### Chair of the Department of Molecular Biology and Immunology at the University of North Texas Health Science Center at Fort Worth

The Graduate School of Biomedical Sciences at the University of North Texas Health Science Center at Fort Worth (UNTHSC) is seeking applications for the position of Professor and Chair of the Department of Molecular Biology and Immunology.

Candidates must possess an M.D., D.O., Ph.D. or equivalent doctoral degree, have academic leadership experience or potential and a proven record of funded research in any of the following areas: biochemistry, cancer biology, oxidative stress and inflammation, microbiology, molecular biology or immunology. The candidate would be expected to recruit several new faculty and to lead the Department into national prominence. The Department of Molecular Biology and Immunology currently has 17 full-time faculty and 29 graduate students. The ongoing research and training activities are supported through multiple federal and non-federal grants. Additional information may be obtained at: <http://www.hsc.unt.edu/departments/mbi/>.

Interested applicants should submit their CV, a letter of interest, and the names and contact information of at least three references to <https://www.unthscjobs.com>. In addition, applicants should send a statement of career objectives electronically to **Dr. Ladislav Dory** at [Lad.Dory@unthsc.edu](mailto:Lad.Dory@unthsc.edu). Applications will be entertained and reviewed until the position is filled.

*UNTHSC is an EEO/Affirmative Action Institution.*

## POSITIONS OPEN



### ASSISTANT PROFESSOR Bacteriology/Microbiology

The Department of Bacteriology at the University of Wisconsin-Madison (UW-Madison, **website:** <http://www.bact.wisc.edu/>) invites applications for a faculty position in Bacteriology/Microbiology at the Assistant Professor level. The Department is interested in candidates working at the cutting edge of microbiology in the general area of microbial physiology in any domain of life. The University and Department provide an excellent environment for the development of an outstanding research program. The successful candidate will be expected to develop a vigorous, extramurally funded, independent research program and to participate in undergraduate and graduate teaching. The position carries a commitment to resident instruction, research, and professional and university service as appropriate to the position and rank.

**Application Procedure:** All applications should be submitted in PDF format to **e-mail:** [facultysearch@bact.wisc.edu](mailto:facultysearch@bact.wisc.edu). Applications should be sent as a single PDF that includes a cover letter referencing **position vacancy listing #74177** (**website:** [http://www.ohr.wisc.edu/pv1/pv\\_074177.html](http://www.ohr.wisc.edu/pv1/pv_074177.html)). The application should include curriculum vitae, list of publications, a brief summary of accomplishments, and directions for future research. Materials should be addressed to Bacteriology Faculty Search Committee. Please ask three references to submit letters of reference to the same e-mail address with the applicant's name in the header. All application materials should be received by November 1, 2012 to ensure full consideration.

*UW-Madison is an Equal Opportunity/Affirmative Action Employer. We promote excellence through diversity and encourage all qualified individuals to apply.*

### TENURE-TRACK POSITIONS The University of Texas Southwestern Medical Center

**ASSISTANT PROFESSORS:** The Department of Physiology invites outstanding scientists with Ph.D., M.D., or equivalent degrees to apply for tenure-track assistant professor positions. Candidates who use innovative optical, mechanical, electrical, molecular biological or computational methods with important applications to physiological systems, ranging from individual genes and proteins to cells and organs are encouraged to apply. However, the scientific excellence of the candidates is more important than the specific area of research.

These positions are part of the continuing growth of the Department at one of the country's leading academic medical centers and will be supported by significant laboratory space on our new campus, competitive salaries, and exceptional startup packages. The University of Texas Southwestern (UT Southwestern) Medical Center is the scientific home to five Nobel Prize Laureates and many members of the National Academy of Sciences and Institute of Medicine. UT Southwestern conducts more than 3,500 research projects annually totaling more than \$417 million.

Applicants should submit curriculum vitae, a brief statement of research plans, and arrange to have three letters of reference sent to: **James Stull, Ph.D., c/o Ronald Doris, Department of Physiology, The University of Texas Southwestern Medical Center, 5323 Harry Hines Boulevard, Dallas, TX 75390-9040.**

*UT Southwestern strongly encourages applications from women, minorities, and people with physical challenges. UT Southwestern is an Equal Opportunity/Affirmative Action Employer.*

**RESEARCH SCIENTIST** (San Diego, California): Prepare reports on development and characterization of cellular and molecular analysis. Assemble, maintain, and operate cytometers. Requirements: Master's degree in Electronic Engineering with Minor in Biomedical Sciences. Send resume to: **La Jolla Bioengineering Institute, 3535 General Atomics Court, Suite 210, San Diego, CA 92121; or fax: 858-456-7540.**

## POSITIONS OPEN

### CELLULAR/MOLECULAR NEUROSCIENCE

The Department of Biology at Indiana University-Purdue University Indianapolis (IUPUI) invites applications for a tenure-track **FACULTY POSITION** in Cellular or Molecular Neuroscience to begin August 1, 2013. Rank is open and competitive salary and startup funds are available. The successful candidate will be involved in helping to shape a new interdisciplinary Neuroscience B.S. program within the School of Science. A Ph.D. and postdoctoral experience in neuroscience or a related area is expected. Applicants must demonstrate the ability to initiate and sustain an externally funded program of research, the potential for successful student mentoring and the ability to teach courses in neuroscience at the graduate and undergraduate levels. Applicants at a senior level must have a record of research excellence, a history of external funding, and a strong record of mentoring students.

Interested individuals are encouraged to apply electronically to **e-mail:** [neurobio@iupui.edu](mailto:neurobio@iupui.edu) by sending a cover letter, curriculum vitae, and a statement of research and teaching interests and background. Candidates should also arrange to have three letters of recommendation sent to the same address. Alternatively, materials can be sent to: **Neuroscience Search Committee, Department of Biology, 723 W. Michigan Street, SL-306, Indianapolis, IN 46202.** Evaluation of completed applications will begin approximately November 1, 2012 and continue until the position is filled.

The IUPUI campus located in downtown Indianapolis has a student population in excess of 30,000 and attracts more external research funding than any other university campus in the State of Indiana. The Department of Biology has a strong record of externally funded research and training of Ph.D. students. The department occupies well-equipped research laboratories and core facilities, which will be significantly expanded with the completion of a new research building in 2014. IUPUI is home to a large and vibrant community researchers in all areas of neuroscience.

*IUPUI is an Equal Employment Opportunity/Affirmative Action Employer with a strong commitment to increasing faculty diversity—we seek to attract a diverse applicant pool for this position, including women and members of minority groups.*

### ASSISTANT OR ASSOCIATE PROFESSOR of Pharmacogenomics

The Department of Pharmaceutical and Biomedical Sciences in the South Carolina College of Pharmacy (**website:** <http://www.sccp.sc.edu>) invites applications from outstanding scientists for a twelve-month full time, faculty position at the level of tenure-track Assistant Professor or tenure-track or tenured Associate Professor in Pharmacogenomics. Applicants should have a Ph.D. or equivalent degree, substantial postdoctoral experience, and a strong record of research accomplishments. The candidate will be expected to develop a strong, extramurally funded research program in Pharmacogenomics, have excellent oral and written communication skills, and participate in graduate and professional education. Salary is competitive and commensurate with experience. The Department has faculty members in Columbia, SC (University of South Carolina) and in Charleston, SC (Medical University of South Carolina). The primary appointment is on the Columbia campus, with a joint appointment on the Charleston campus.

Interested candidates should apply directly through the University of South Carolina jobs **website:** <https://uscjobs.sc.edu/>. The requisition number for this position is **005268**. As part of your application please include curriculum vitae, a statement of research interests, a statement of teaching interests, and the names of at least three references. Any questions concerning this position should be sent electronically to **Dr. Kim E. Creek, Vice-Chair, Department of Pharmaceutical and Biomedical Sciences, University of South Carolina, at e-mail:** [creekk@sccp.sc.edu](mailto:creekk@sccp.sc.edu). Applications will be reviewed continuously until the position is filled.

*The University of South Carolina is an Affirmative Action/Equal Opportunity Employer and specifically invites and encourages applications from women and minorities.*

## POSITIONS OPEN

### TENURE-TRACK ASSISTANT PROFESSOR

#### Animal Physiology Rollins College Winter Park, FL

The Department of Biology at Rollins College invites applications for a tenure-track assistant professor position in animal physiology beginning August 2013. Ph.D. and postdoctoral experience required. The successful candidate must be prepared to teach upper-level undergraduate animal and human physiology. The successful candidate will also teach general biology for majors and a general education course for non-majors. Preference is given to candidates who specialize in health-related research and are broadly trained in vertebrate physiology. The candidate will also be expected to initiate and sustain a research program involving undergraduate students.

Review of applications will begin October 15, 2012 and continue until the position is filled. Interested applicants must apply online via the College's employment **website:** <http://www.rollinsjobs.com>, and upload the following materials merged together into electronic files as follows: (1) a letter of interest, including a statement of teaching philosophy, (2) curriculum vita and transcripts, (3) research summaries with a list of non-routine equipment needs for research.

Three letters of recommendation should be sent to: **Dr. Paul Stephenson, Chair, Department of Biology, 1000 Holt Avenue, Rollins College, Winter Park, FL 32789; e-mail:** [pstephenson@rollins.edu](mailto:pstephenson@rollins.edu). Questions may be directed to the same address.

Founded in 1885, Rollins is an independent, comprehensive, liberal arts college. The campus, noted for its lakefront beauty and for its unique location, is set in the residential community of Winter Park, just 15 minutes from one of the nation's most dynamic urban centers, Orlando. Rollins enrolls approximately 3,200 students in diverse degree programs at the undergraduate and graduate level. Rollins ranks number one among 128 Southern Master's-level universities in the annual rankings of "America's Best Colleges," released by U.S. News & World Report. For additional information, please visit the College **website:** <http://www.rollins.edu> and the Department of Biology **website:** <http://www.rollins.edu/biology>.

*Through its mission, Rollins College is firmly committed to creating a just community that embraces multiculturalism; persons from historically underrepresented minority groups are therefore encouraged to apply.*

### FACULTY APPOINTMENT in Cell Biology Department of Cell Biology Duke University Medical Center

The Department of Cell Biology at Duke University Medical Center is hiring a tenure-track faculty member. The preferred level is for an **ASSISTANT PROFESSOR** who would start his/her independent career at Duke. Candidates with demonstrated expertise in stem cell biology, tissue regeneration, or animal cell structure/function are especially encouraged to apply. Preference will be given to candidates whose activities complement and strengthen research programs within the department. Successful candidates will have track records of creativity and productivity, demonstrated potential for outstanding future achievements, and a desire to participate in an exciting, interactive, and growing community. They will be expected to mount a productive and innovative research program, to obtain outside funding, and to participate actively in graduate training. Candidates must have a Ph.D., M.D., or equivalent degree. Qualified minority candidates are especially encouraged to apply. For full consideration, application should be submitted by December 1, 2012, although applications will be considered until the position is filled. Applicants should submit curriculum vitae, a brief summary of current and proposed research, and three letters of recommendation to **website:** <https://academicjobsonline.org/ajo/jobs/1810>.

Questions may be directed to **Dr. Brigid Hogan, Chair, Department of Cell Biology, (e-mail:** [brigid.hogan@duke.edu](mailto:brigid.hogan@duke.edu)).

*Duke University is an Equal Opportunity/Affirmative Action Employer.*

## Assistant or Associate Professor



The Department of Cancer Biology at the Perelman School of Medicine at the University of Pennsylvania seeks candidates for an Assistant, Associate, and/or Full Professor position in the tenure track. Rank will be commensurate with experience. The successful applicant will have experience in the field of cancer biology, including but not limited to cancer genetics and genomics, tumor microenvironment, epigenetics, angiogenesis, cancer cell metabolism and oncogenic signaling. Responsibilities include the development of an independent research program. Teaching duties comprise mentoring students and course lecturing. Applicants must have an M.D. and/or Ph.D. degree and have demonstrated excellent qualifications in research and education.

We seek candidates who embrace and reflect diversity in the broadest sense.

The University of Pennsylvania is an equal opportunity, affirmative action employer.

Apply for this position online at:

[http://www.med.upenn.edu/apps/faculty\\_ad/index.php/d3035](http://www.med.upenn.edu/apps/faculty_ad/index.php/d3035)

Contact Information:

Lewis A. Chodosh, MD, PhD  
J. Samuel Staub Professor  
Chair, Department of Cancer Biology  
Perelman School of Medicine  
University of Pennsylvania  
612 BRB II/III, 421 Curie Boulevard,  
Philadelphia, PA 19104-6160



## Faculty Opening for Division Chief July, 2012

The Department of Radiation Oncology at UT Southwestern Medical Center seeks an exceptional senior scientist to head the department's division of Molecular Radiation Biology. Applicants must have a Ph.D. or M.D./Ph.D. and a vigorous and ambitious independent research program in an area of cancer biology that is related to radiation oncology, as well as grant funding and a significant record of peer-reviewed publication. The program should complement and expand existing research strengths within the division, which includes molecular oncology, cell signaling, hypoxia and the DNA damage response. Candidates should have a successful record as the manager of a productive research team and an enthusiasm for promoting collaboration within a multidisciplinary environment.

The Division of Molecular Radiation Biology currently has 60 employees, including seven senior Ph.D. investigators and three M.D./Ph.D. translational researchers as well as other junior research faculty, postdoc and graduate student trainees, and lab technicians. There is also significant dedicated administrative support staff. The division has approximately 10,000 square feet of contiguous lab space, including 6 large labs and core space for tissue culture, microscopy, and other shared resources.

The appointment will be at the level of Professor, with tenure (contingent upon approval by the institutional promotion and tenure committee). A generous start up package will include substantial lab space and funding for equipment or faculty/staff/trainees. Of particular note, the Cancer Prevention and Research Institute of Texas (CPRIT) has awarded over \$106 million in grants to investigators at UT Southwestern, including funding opportunities for recruitment of pre-eminent cancer investigators.

Applicants should email their curriculum vitae, the names of three references, and a brief description of their research goals to the attention of **Dr. Hak Choy** at [Hak.Choi@utsouthwestern.edu](mailto:Hak.Choi@utsouthwestern.edu).

*UT Southwestern is an Equal Opportunity Employer.*



### University of Utah Huntsman Cancer Institute Department of Oncological Sciences

The **Department of Oncological Sciences** and **Huntsman Cancer Institute** (HCI) invite applications for a tenure-track faculty position at the **assistant or associate professor** level. We seek an outstanding **Bioinformatician** with a program focused in genome sciences, including the development of methods for analyzing genome-wide data derived from high-throughput sequencing. Requirements include a PhD or MD/PhD and a track record of scientific excellence. Areas of interest could include transcription/epigenetic regulation, cancer gene/mutation discovery, or the use of genomics in cancer diagnostics. Departmental strengths include epigenetics and transcriptional regulation, mouse and zebrafish models of cancer, and cancer cell biology—including signaling, apoptosis, DNA repair, motility, and metabolism. HCI is an NCI-designated cancer center with state-of-the-art laboratories and shared resources, including core facilities for imaging, genomics, drug screening, and population studies. We offer a collegial and interactive research environment that fosters the development of junior faculty and robust graduate programs for training PhD and MD/PhD students.

Candidates are encouraged to apply by **November 9, 2012** at the following link: <http://utah.peopleadmin.com/postings/18172>.

*The University of Utah is an Equal Opportunity/Affirmative Action employer and educator. Minorities, women, and persons with disabilities are strongly encouraged to apply. Veterans' preference. Reasonable accommodations provided. For additional information, visit <http://www.regulations.utah.edu/humanResources/5-106.html>.*

*The University of Utah values candidates who have experience working in settings with students from diverse backgrounds and possess a strong commitment to improving access to higher education for historically underrepresented students.*



### University of Utah Huntsman Cancer Institute Department of Oncological Sciences

The **Department of Oncological Sciences** and **Huntsman Cancer Institute** (HCI) invite applications for a tenure-track faculty position at the **assistant or associate professor** level. We seek an outstanding **basic cancer biologist** with an interest in one or more of the following areas: transcriptional networks, stem cell transcriptional circuitry, chromatin regulation, or RNA biology—with a genome-wide perspective. Requirements include a PhD or MD/PhD and a track record of scientific excellence. Departmental strengths include epigenetics and transcriptional regulation, human cancer genetics, mouse and zebrafish models of cancer, and cancer cell biology—including signaling, apoptosis, DNA repair, motility, and metabolism. HCI is an NCI-designated cancer center with state-of-the-art laboratories and shared resources including core facilities for imaging, genomics, drug screening and in vivo testing, and population studies. We offer a collegial and interactive research environment that fosters the development of junior faculty and robust graduate programs for training PhD and MD/PhD students.

Candidates are encouraged to apply by **November 9, 2012** at the following link: <http://utah.peopleadmin.com/postings/18166>.

*The University of Utah is an Equal Opportunity/Affirmative Action employer and educator. Minorities, women, and persons with disabilities are strongly encouraged to apply. Veterans' preference. Reasonable accommodations provided. For additional information, visit <http://www.regulations.utah.edu/humanResources/5-106.html>.*

*The University of Utah values candidates who have experience working in settings with students from diverse backgrounds and possess a strong commitment to improving access to higher education for historically underrepresented students.*



## POSITIONS OPEN



### FACULTY POSITION in Viral Oncology The Ohio State University

The Department of Veterinary Biosciences ([website: http://vet.osu.edu/biosciences](http://vet.osu.edu/biosciences)) in the College of Veterinary Medicine, seeks outstanding candidates for a tenure-track position at the Assistant/Associate Professor level. Candidates must have a Ph.D., D.V.M., M.D., or equivalent degree and demonstrated accomplishment in research focused on oncogenic viruses (e.g., retroviruses, herpesviruses, papillomaviruses, hepadnaviruses). Candidates with research experience that complements existing programs ([website: http://lsn.osu.edu/research-centers](http://lsn.osu.edu/research-centers)) within the Center of Retrovirus Research and the Ohio State University Comprehensive Cancer Center would be particularly welcome. The Department offers excellent laboratory facilities, competitive salary and startup package, and access to numerous core facilities including state-of-the-art BSL-3 facilities. Successful candidates will be expected to have or to develop a sustainable extramurally funded research programs and to contribute to professional (DVM), graduate and undergraduate education.

Applications should be submitted via e-mail as a single PDF document and include a curriculum vitae, summary of research program and future directions, and the names (with complete mailing, phone, and e-mail address) of at least four individuals from whom letters of reference may be solicited. Review of applications will begin November 15, 2012 and continue until the position is filled. Address all correspondence to **Dr. Stefan Niewiesk**, Chair of the Search Committee (e-mail: [niewiesk.1@osu.edu](mailto:niewiesk.1@osu.edu)).

*The Ohio State University is an Equal Opportunity/Affirmative Action Employer. Minorities, Veterans, Women, and individuals with disabilities are encouraged to apply.*

### FACULTY POSITIONS IN BIOCHEMISTRY University of Notre Dame

The Department of Chemistry and Biochemistry at the University of Notre Dame invites applications for tenure-track positions in all areas of biochemistry and molecular biology. Exceptional candidates at all levels are encouraged to apply. Candidates must provide a cover letter, curriculum vitae, a detailed research plan, and a statement of teaching interests. Junior candidates must also arrange for at least three letters of recommendation, while senior applicants can apply in confidence. All materials should be submitted to the application [website: https://academicjobsonline.org/ajo/jobs/1750](https://academicjobsonline.org/ajo/jobs/1750). Applications must be received by October 15, 2012 to receive full consideration.

*The University of Notre Dame, an Equal Opportunity Employer with a strong institutional and academic commitment to diversity, endeavors to foster a vibrant learning community animated by the Catholic intellectual tradition.*

### TENURE-TRACK ASSISTANT PROFESSOR Washington University Center for the Study of Itch

Center for the Study of Itch (CSI, visit [website: http://csi.wustl.edu](http://csi.wustl.edu) for information), a newly established multidisciplinary center, invites outstanding candidates to apply for tenure-track assistant professor positions. Candidates are expected to develop independent and innovative research programs focusing on itch. Candidates without prior experience in itch but plan to pursue the study of itch are encouraged to apply. Areas of interest include but not limited to: somatosensations, pain and itch electrophysiology, cutaneous biology, and dermatology. Applicants should submit curriculum vitae, a summary of research experience, and a future research plan to **Dr. Zhou-Feng Chen** at e-mail: [chenz@wustl.edu](mailto:chenz@wustl.edu), or **Center for the Study of Itch**, Campus Box 8054, Washington University School of Medicine, Street Louis, MO 63110, U.S.A. Application deadline December 15, 2012. *Washington University is an Equal Opportunity Employer including Minorities/Females/Persons with Disabilities/Veterans.*

## POSITIONS OPEN

### IOWA STATE UNIVERSITY

#### TWO ASSISTANT PROFESSOR POSITIONS in Systems Biology and Plant Evolutionary Genomics Iowa State University

The departments of Genetics, Development and Cell Biology (GDCB) and Ecology, Evolution & Organismal Biology (EEOB) at Iowa State University invite applications for two tenure-track positions at the Assistant Professor level. We seek creative individuals employing genomic or interdisciplinary approaches to address fundamental questions. The GDCB position focuses on biological networks that mediate cellular, metabolic, or developmental processes (see [website: http://www.gdcb.iastate.edu/about\\_dept/jobvacancies.shtml](http://www.gdcb.iastate.edu/about_dept/jobvacancies.shtml)), whereas the EEOB position is in plant evolutionary genomics (see [website: http://www.eeob.iastate.edu/search.html](http://www.eeob.iastate.edu/search.html)). Successful candidates will join dynamic departments embedded in a highly integrative and collaborative campus. Applicants must have a Ph.D. and are expected to establish nationally recognized, externally funded programs of research and to contribute skillfully to undergraduate and graduate courses.

Application instructions are at [website: http://www.iastatejobs.com](http://www.iastatejobs.com) (vacancies 120902 and 120903). Applicants should submit a cover letter, curriculum vitae, research and teaching statements, and up to three reprints by 12 October 2012. Submission of three confidential letters of recommendation should be arranged as per instructions in the online application system.

*Iowa State University promotes excellence through diversity and is an Affirmative Action/Equal Employment Opportunity Employer with an ADVANCE program to enhance the success of women faculty and faculty of color in science and engineering.*

#### ASSISTANT PROFESSOR

The Roy J. Carver Department of Biochemistry, Biophysics, and Molecular Biology at Iowa State University is embarking on a transformational expansion of its structural biology research enterprise through a large philanthropic gift from the Roy J. Carver Charitable Trust. This major research initiative in Biomolecular Structure includes long-term investment in new instrumentation, endowed funds for graduate student training, and a series of new faculty hires working at the forefront of any aspect of structural biology. As the first of several faculty positions associated with this Initiative, and as part of an interdisciplinary effort across the Iowa State campus to expand structural biology research, the Department seeks a new tenure-track assistant professor to establish a vibrant, externally funded research program of international prominence and participate in graduate and undergraduate teaching.

Applicants should have a Ph.D. or equivalent degree and appropriate research experience. To view entire vacancy #120765 and apply, create an electronic application at [website: http://www.iastatejobs.com](http://www.iastatejobs.com). To guarantee consideration the applications must be received by November 1, 2012.

*Applications from women and members of underrepresented groups are strongly encouraged. Iowa State University is an Equal Opportunity/Affirmative Action Employer.*

#### ASSISTANT PROFESSOR

Penn State Wilkes-Barre invites applications for an Assistant Professor of Biology to begin August 2013. Teach human anatomy and physiology at the undergraduate level. Ability to teach basic chemistry is a plus. Publication of research in referred journals and service activities expected. Ph.D. in biology or a closely related area is required. To learn about the campus and Penn State University, visit [website: http://www.psu.edu/hr/cmpcoll.html](http://www.psu.edu/hr/cmpcoll.html). To learn more about the position and how to apply, visit [website: http://www.psu.jobs/Search/Opportunities.html](http://www.psu.jobs/Search/Opportunities.html) and follow the "Faculty" link. *Affirmative Action/Equal Opportunity Employer.*

## POSITIONS OPEN



### TENURE-TRACK FACULTY POSITION

The BioFrontiers Institute at the University of Colorado in Boulder is looking for its next interdisciplinary faculty member.

We invite applications from candidates seeking to develop an internationally recognized research program that addresses significant problems in biology and medicine at the interface with the physical sciences, mathematics, and/or computer science.

BioFrontiers integrates faculty from the departments of Chemistry & Biochemistry; Molecular, Cellular & Developmental Biology; Ecology & Evolutionary Biology; Physics; Integrative Physiology; Applied Mathematics; Computer Science; Chemical & Biological Engineering; and Mechanical Engineering. A successful candidate could choose to be rostered in any of these departments.

The position is at the ASSISTANT PROFESSOR level, although senior candidates at ASSOCIATE and FULL PROFESSOR ranks will also be considered. Candidates must have a Ph.D. and a demonstrated commitment to teaching at undergraduate and graduate levels.

Learn more and apply online at [website: http://BioFrontiers.colorado.edu/facultyhire](http://BioFrontiers.colorado.edu/facultyhire). Review of applications will begin on November 1, 2012 and will continue until the position is filled. Application materials are accepted electronically at [website: https://www.jobsatcu.com/applicants/Central?quickFind=70421](https://www.jobsatcu.com/applicants/Central?quickFind=70421) (posting number 819126). *The University of Colorado is committed to diversity and equality in education and employment and sensitive to the needs of dual career couples. The University of Colorado is an Equal Opportunity Employer.*

### FACULTY POSITION

California Institute of Technology invites applications for a tenure-track faculty position in the Division of Chemistry and Chemical Engineering at the ASSISTANT PROFESSOR level in the area of chemical engineering. Candidates with strong commitments to research and teaching excellence are encouraged to apply. The term of the initial appointment is normally four years and is contingent upon completion of all requirements for a Ph.D. in chemical engineering or in a related field. Each application should include curriculum vitae, publication list, a description of proposed research, and three letters of recommendation, and should be sent electronically (e-mail: [search@chem.caltech.edu](mailto:search@chem.caltech.edu)) to: **Chair of the Chemical Engineering Search Committee, M/C 210-41, California Institute of Technology, Pasadena, CA 91125**. Applications should be received by October 15, 2012. *The California Institute of Technology is an Equal Opportunity/Affirmative Action Employer. Women, minorities, veterans, and disabled persons are encouraged to apply.*

### FACULTY POSITION

California Institute of Technology invites applications for a tenure-track faculty position in the Division of Chemistry and Chemical Engineering at the ASSISTANT PROFESSOR level in the areas of biochemistry, chemical biology, or inorganic chemistry. Candidates with strong commitments to research and teaching excellence are encouraged to apply. The term of the initial appointment is normally four years and is contingent upon completion of all requirements for a Ph.D. in chemistry or in a related field. Submit curriculum vitae, publication list, a description of proposed research, and three letters of recommendation electronically to Chair of the Search Committee, e-mail: [ceesrch@caltech.edu](mailto:ceesrch@caltech.edu). Applications should be received by November 1, 2012. *The California Institute of Technology is an Equal Opportunity/Affirmative Action Employer. Women, minorities, veterans, and disabled persons are encouraged to apply.*



# Pomona College

## PLANT BIOLOGY

The Biology Department at Pomona College, a member of the Claremont Colleges, invites applications for a tenure-track position at the level of Assistant Professor in the area of Plant Physiology, Plant Physiological Ecology, or Plant Development, beginning July 1, 2013. Candidates must have a Ph.D. and postdoctoral experience. Teaching responsibilities will include an introductory course in Cellular Chemistry and Cell Biology, an upper-level laboratory course in Plant Physiology, and potentially another upper-level laboratory course. The appointee will be expected to initiate and sustain a productive research program that involves undergraduates. We are particularly interested in candidates who have a demonstrated commitment to improving success in higher education for underrepresented students.

Please submit the following application materials online (<https://academicjobsonline.org/ajob/jobs/1711>): cover letter, curriculum vitae, a statement of teaching philosophy and interests, a summary of research plans, and three letters of reference. You may address your cover letter to Prof. Len Seligman, Chair of the Search Committee. Complete applications received by **October 8, 2012** will receive full consideration.

*Pomona College is an Equal Opportunity Employer and especially invites applications from women and members of underrepresented groups.*

# ASU SCHOOL OF Life Sciences

## ARIZONA STATE UNIVERSITY

## Senior Faculty Position in Biology Education

Arizona State University is a dynamic, progressive university dedicated to interdisciplinary collaborations, to rethinking university education, and to integrating excellence in both research and teaching. The School of Life Sciences at Arizona State University's Tempe campus is committed to reflective curricular development, with a focus on learner-centered education and teaching excellence. To support this effort, the School invites applications for a tenure-track position at the Associate or Full Professor level, to be appointed within the School of Life Sciences and to work collaboratively with science education initiatives in the Mary Lou Fulton Teachers College.

Candidates must have a Ph.D. in the life sciences or education with experience/training equivalent to a Master's degree in the other area. Candidates must demonstrate a primary research focus in teaching and learning in biology at the post-secondary level; strong disciplinary content knowledge in biological sciences; established expertise in and commitment to biology education; and evidence of leadership. Candidates must also demonstrate excellence in promoting quality undergraduate instruction through independent and collaborative efforts; scholarly excellence with the capacity to develop and sustain a creative, extramurally-funded research program; evidence of interdisciplinary collaboration; and a record of mentoring. The start-up package, teaching, and service loads will support the expected high research productivity. A strong record of outreach and service, and experience working in a highly interdisciplinary environment like the ASU School of Life Sciences are desired.

To apply, please send a cover letter, curriculum vitae, three representative publications, separate statements of research focus/plans, teaching philosophy/experience, and contact information for three references to **Anna Fields, ATTN: Biology Education Faculty Search Committee, School of Life Sciences, PO Box 874501, Tempe, AZ 85287-4501**, with electronic applications sent as PDF files to [solsfacultysearch@asu.edu](mailto:solsfacultysearch@asu.edu) preferred. The initial closing date for receipt of complete applications is **October 14, 2012**. Applications will be reviewed weekly thereafter until the search is closed. For additional information, please feel free to contact **James Collins** ([jcollins@asu.edu](mailto:jcollins@asu.edu)) or **Jane Maienschein** ([maienschein@asu.edu](mailto:maienschein@asu.edu)). For additional information on this position and the School of Life Sciences, please visit <https://sols.asu.edu>.

*A background check is required for employment at Arizona State University, which is an Equal Opportunity/Affirmative Action Employer committed to excellence through diversity. We especially encourage women and minorities to apply.*

# BSi

Brain Science Institute  
Johns Hopkins Medicine



JOHNS HOPKINS  
MEDICINE

## Assistant Professor Positions Brain Science Institute

Applications are invited for tenure-track faculty positions in the Brain Science Institute at the Johns Hopkins University School of Medicine (<http://www.brainscienceinstitute.org>). Applicants should have interests in synapses and circuits in normal brain function or in cognitive disorders such as autism, schizophrenia and Alzheimer's disease. Applicants should have a Ph.D. or M.D., and a strong record of research accomplishments. Faculty will receive primary appointments in a relevant department such as Neuroscience, Neurology or Psychiatry. Faculty members are expected to establish creative active independent research programs and participate in teaching graduate and medical students. Deadline for applications is **November 1st, 2012**. Please submit a PDF file containing CV and a brief description of current and future research interests and arrange for three letters of reference to be sent on your behalf.

**Richard L. Haganir**  
Chair Search Committee  
Brain Science Institute  
The Johns Hopkins University  
School of Medicine  
725 North Wolfe Street, Hunterian 1009A  
Baltimore, Maryland 21205  
[HopkinsBSiSearch@jhmi.edu](mailto:HopkinsBSiSearch@jhmi.edu)

*The Johns Hopkins University is committed to enhancing the diversity of its faculty and encourages applications from women and minorities.  
An EEO/AA Employer.*

# University of Nevada School of Medicine

## INFECTIOUS DISEASES/ MICROBIOLOGY AND IMMUNOLOGY

The University of Nevada School of Medicine is seeking candidates for an Infectious Diseases/Microbiology and Immunology physician, tenure-track full-time faculty appointment at the Assistant or Associate Professor level. Candidates with research interest in infectious disease or immunology are especially encouraged to apply. The successful faculty candidate is expected to maintain a vigorous independent research program in the Infectious Diseases Division within the Department of Internal Medicine and participate actively in the teaching, research, and graduate training programs in the departments of Microbiology & Immunology and Internal Medicine. In addition, a secondary academic appointment will be in the Department of Microbiology and Immunology, Reno. The appointment will also involve serving as an infectious disease clinician (no more than 10 percent of time allotment). Generous and competitive startup funds including salary support and dedicated research space in the Department of Microbiology & Immunology are available.

Requirements: M.D., MD/Ph.D. or D.O. degree or equivalent with a focus in infectious disease or immunology and must have completed an ACGME-approved Internal Medicine residency program and a fellowship prior to start date. Candidates must be eligible for an unrestricted Nevada medical license, malpractice insurance, and must be able to be successfully credentialed by Northern Nevada teaching hospitals. Applicants for an Associate Professorship must have national research funding.

For more information and to apply, please visit <http://apptkr.com/271002>

AA/EOE





## Georgia Health Sciences University

### FACULTY POSITIONS in Systems Neuroscience

The Brain and Behavior Discovery Institute (BBDI) at the Georgia Health Sciences University (GHSU) is seeking up to six faculty members who will be appointed as tenure-track **ASSISTANT PROFESSOR**, tenured **ASSOCIATE PROFESSOR** or **FULL PROFESSOR**. Candidates should have a Ph.D. or M.D. degree with a strong record of research accomplishment working in systems neuroscience. Approaches using molecular genetics, in vivo imaging, neural recordings, optogenetics, circuits mapping, or large-scale neural computation/modeling, are highly encouraged. Faculty members are expected to establish or have creative, cutting-edge research programs and may participate in teaching medical and graduate students. GHSU is a state supported academic medical center located in a historic city with outstanding recreational and lifestyle opportunities.

Consideration of candidates is ongoing and will continue until the search has been successfully concluded. Please submit curriculum vitae, a statement of current and future research interests, and arrange three letters of recommendation to:

Joe Z. Tsien, Ph.D.  
Neuroscience Faculty Search  
The Brain and Behavior Discovery Institute (BBDI)  
School of Medicine  
Georgia Health Sciences University  
1120 15th Street, CL-3033  
Augusta, GA 30912-4750  
ATTN: Toni Goodly  
E-mail: lgoodly@georgiahealth.edu

You are also required to complete an online application at website: <http://www.mcg.edu/facultyjobs/> (req #s 4780, 4781, 4782, 4783, 4784, 4785, 4786, 4788.) Equal Employment Opportunity/Affirmative Action/Equal Access Employer.

### ORGANIC AND BIOLOGICAL CHEMISTRY Dartmouth College

Applications are invited for two faculty positions starting July 2013, one at the tenured **ASSOCIATE** or **FULL PROFESSOR** level, and one at the rank of **ASSISTANT PROFESSOR**. The Chemistry Department seeks a senior individual who has already established a nationally recognized research program in synthetic organic chemistry, together with a junior colleague in biological chemistry, broadly defined, both of whose research interests will complement those of the current faculty, and who will excel at teaching in our undergraduate and Ph.D. curriculum. We particularly seek candidates who will help lead, initiate, and participate in collaborative research projects both within Chemistry and involving other Dartmouth researchers, including those at Dartmouth's Geisel School of Medicine, Norris Cotton Cancer Center, and Thayer School of Engineering. Candidates will be expected to teach introductory and advanced undergraduate courses in organic chemistry or biochemistry, as well as graduate courses in their area of research. Applicants should submit curriculum vitae, a description of their current research funding (where appropriate) and future plans, and a statement of their teaching interests, and should arrange for three recommendation letters to be submitted. All inquiries and applications will be treated confidentially. Application materials should be uploaded as a single PDF at website: <http://caligari.dartmouth.edu/~chem/>. The Committee will begin to consider completed applications on October 15. *With an even distribution of male and female students and over a quarter of the undergraduate student population members of minority groups, Dartmouth is committed to diversity and encourages applications from women and minorities.*

## UNIVERSITY OF LOUISVILLE

### ASSISTANT/ASSOCIATE PROFESSOR

The Institute of Molecular Cardiology at the University of Louisville is seeking qualified candidates to join the members of the Institute in work focusing on cell therapy for myocardial repair. Appointments will be at Assistant/Associate Professor level depending on qualifications. The successful candidate will have a track record of working with stem/progenitor cells in the cardiovascular system. He/she will join a productive, highly collegial, and multidisciplinary team of investigators supported by state-of-the-art facilities and considerable funds. Submit letter of application with a curriculum vitae and statement of interest to: **Dr. Roberto Bolli, 550 S. Jackson Street, ACB, Third Floor, Louisville, KY 40202.** Affirmative Action/Equal Opportunity Employer.

### THREE OPEN FACULTY POSITIONS Boston College Chemistry Department

The Chemistry Department of Boston College invites applications for three tenure-track positions to be effective in the Fall of 2013. Applicants will be evaluated based on their potential to establish a prominent and well-funded research program and to excel in teaching at the graduate and undergraduate levels. Successful applicants will join a department of approximately 120 doctoral students, 30 postdoctoral fellows, 200 undergraduate majors, and an internationally recognized faculty.

**ASSISTANT PROFESSORS** in the areas of (broadly defined) Chemical Biology, Organic Chemistry, and Physical/Materials Chemistry: requires a Ph.D. in Chemistry or related areas; postdoctoral experience is desirable but not required. The candidate is expected to have published in top-referenced journals and demonstrated the ability to perform outstanding independent research.

Applicants must submit in one transmission in the form of PDF files to e-mails: [orgchemsearch@bc.edu](mailto:orgchemsearch@bc.edu), [chembiosearch@bc.edu](mailto:chembiosearch@bc.edu), or [pchemsearch@bc.edu](mailto:pchemsearch@bc.edu); a cover letter, a graphical executive summary of research plans (one page), a curriculum vitae, a summary of research plans (eight pages maximum), and a statement of teaching philosophy. In the cover letter, the names of three references should be specified. Applicants should arrange to have three letters of reference in the PDF format transmitted to e-mails: [orgchemsearch@bc.edu](mailto:orgchemsearch@bc.edu), [chembiosearch@bc.edu](mailto:chembiosearch@bc.edu), or [pchemsearch@bc.edu](mailto:pchemsearch@bc.edu); original copies of the letters may be requested by the department.

All application materials must be submitted electronically on or prior to 15 October 2012.

*Boston College, a university of eight schools and colleges, is an Equal Opportunity Employer and supports Affirmative Action.*

### HARVARD UNIVERSITY

The Department of Psychology anticipates making a tenure-track appointment at the **ASSISTANT PROFESSOR** level to begin July 1, 2013.

We seek candidates with exceptional promise in the area of social psychology. Although we are especially interested in candidates whose research focuses on judgment and decision-making, emotion, or social networks, we are less concerned with interests than with excellence.

It is required that candidates will have completed all requirements for the Ph.D. by the start date of the appointment. Teaching duties will include offerings at both undergraduate and graduate levels.

Candidates should submit curriculum vitae, research and teaching statements, representative reprints, and the contact information for at least three references to website: <http://academicpositions.harvard.edu/postings/4177>. Questions regarding this position can be addressed by calling telephone: 617-384-9425. The closing date for applying is October 1.

*Applications from women and minority groups are strongly encouraged. Harvard University is an Affirmative Action/Equal Opportunity Employer.*

### TWO TENURE-TRACK POSITIONS in Neuroscience

The Program in Neuroscience at the College of Wooster invites applications for two tenure-track positions beginning August 2013. One position will be housed in Biology, the other in Psychology. Both successful applicants will contribute to a rapidly growing interdisciplinary Neuroscience major, participate in the First Year Seminar Program, and direct undergraduate research in the required Senior Independent Study Program. We seek committed teacher-scholars with demonstrated excellence in undergraduate teaching and productive research programs that will engage students. The College of Wooster provides significant research support, including startup, travel, faculty development funds, and a generous sabbatical program.

**ASSISTANT PROFESSOR OF BIOLOGY:** Teaching responsibilities will include Cellular Neuroscience, Development, and Introductory Molecular/Cellular Biology. Preference will be given to applicants whose research interests emphasize integrative/physiological approaches. Applicants should have a Ph.D.; postdoctoral research and/or teaching experience preferred. Send curriculum vitae, statements of research and teaching philosophy, graduate and undergraduate transcripts, and three letters of recommendation to e-mail: [biology@wooster.edu](mailto:biology@wooster.edu). Questions concerning this position should be directed to **Dr. M. Lovelless**, Chair of Biology, e-mail: [mlovelless@wooster.edu](mailto:mlovelless@wooster.edu). Electronic applications are preferred, and should be received by October 12, 2012 for full consideration.

**ASSISTANT PROFESSOR OF PSYCHOLOGY:** Teaching responsibilities will include Introductory Psychology, Human Neuropsychology, Introduction to Neuroscience, an Integrative Senior Seminar in Neuroscience, and courses in the candidate's area of specialty. Preference will be given to candidates with training in Human Neuroscience, Ph.D. or ABD required. Send a letter of application, curriculum vitae, graduate transcripts, statements of teaching and research interest, and arrange to have three letters of recommendation sent to e-mail: [psychology@wooster.edu](mailto:psychology@wooster.edu). Questions concerning this position should be directed to **Dr. John Neuhoﬀ**, Chair of Psychology, e-mail: [jneuhoff@wooster.edu](mailto:jneuhoﬀ@wooster.edu). Electronic applications are preferred and should be received by October 19, 2012 for full consideration.

*Wooster seeks to ensure diversity by its policy of employing persons without regard to age, sex, color, race, creed, religion, national origin, disability, veteran status, sexual orientation, or political affiliation. The College of Wooster is an Equal Opportunity/Affirmative Action Employer.*

### ASSISTANT PROFESSOR Evolutionary Ecology

The Department of Biological Sciences, California State University, East Bay (CSUEB), seeks to fill a tenure-track position in Evolutionary Ecology, Fall 2013. We invite applications from individuals who use integrative approaches to investigate the evolutionary mechanisms underlying the responses of organisms to their environment. The position requires the ability to balance teaching responsibilities with professional achievement, to include the development of a student-centered research program in an appropriate model system (e.g., insect or arachnid). Teaching assignments might include Animal Biology, Ecology, and development of upper division and Master's-level courses in the applicant's area of expertise. Ph.D. and postdoctoral experience required; teaching experience preferred. Submit the following in hard copy: An introductory letter that includes separate research and teaching statements, curriculum vitae, reprints of major publications, and three letters of recommendation, all addressed to: **Evolutionary Ecologist Search Committee, Department of Biological Sciences, California State University, East Bay, 25800 Carlos Bee Boulevard, Hayward CA 94542.** Cite position number 13-14 BIOL-EVOLECOLOGY-TT. Contact the Search Committee Chair via e-mail: [erica.wildy@csueastbay.edu](mailto:erica.wildy@csueastbay.edu) with your question. Review of applications begins November 9, 2012 and continues until the position is filled. CSUEB, an Equal Opportunity Employer, is committed to the principles of diversity in employment.





**MICROBIAL/MOLECULAR  
BIOLOGIST**  
Department of Biology The  
Catholic University of America

The Department of Biology has a tenure-track opening at the level of **ASSISTANT PROFESSOR** in the general area of microbiology. Applications are sought from candidates using multifaceted mechanistic approaches to study an exciting problem in a prokaryote or simple eukaryote such as mechanisms of infectious disease and pathogenesis, host inflammatory response, or host-pathogen interactions. The successful candidate will join a collegial research-oriented department that offers undergraduate and graduate (M.S. and Ph.D.) programs. The new faculty member is expected to pursue an extramurally-funded research program and teach undergraduate microbiology as well as develop specialty courses for graduate students. Information about the Department and faculty research interests can be found at: <http://biology.cua.edu>. Please send curriculum vitae, statement of research and teaching interests, and three letters of reference to: **Dr. Ann Corsi, Department of Biology, 103 McCort-Ward Bldg, 620 Michigan Avenue NE, Washington, DC 20064**. Applications will be reviewed as they are received but should be submitted by **October 31, 2012**.

*The Catholic University of America is the national university of the Catholic Church and was founded as a center of research and scholarship. We seek candidates who, regardless of their religious affiliation, understand and will make a significant contribution to the university's mission and goals. CUA is an Affirmative Action/Equal Opportunity Employer.*



**Washington State University – Institute of  
Biological Chemistry Assistant  
Professor or Associate Professor in Plant  
Biology/Plant Biochemistry**

Applications are invited for a full-time, 9 month, tenure-track, (100% Agricultural Research Center) position to begin August 16, 2013 or as negotiated at the Pullman, WA campus. Applicants must have a Ph.D. or equivalent, as well as at least one year postdoctoral experience by start date.

Washington State University's Agricultural Research Center (ARC) has launched a strategic initiative to enhance its plant science research capacity and especially to increase the speed of breeding valuable traits into agriculturally important crops for Washington State in order to respond to anticipated new markets, diseases, pests, and environmental changes. The successful candidate for this position will be expected to rapidly develop a highly competitive research program and contribute substantially to the missions of the ARC, the Institute of Biological Chemistry, and College of Agricultural, Human, and Natural Resource Sciences. Candidates should demonstrate quality and quantity of research accomplished in a fundamental area of modern plant science; and employ as needed innovative approaches in plant biochemistry/biophysics, structural biology, systems biology, and phenomics/phenotyping in key strategic areas of plant metabolism, growth and development, a coherent research plan that incorporates these approaches, and excellent oral and written communication skills. A major objective of their work should be to speed development of improved crop varieties. The candidate will also be expected to teach graduate students in the area of modern plant biology/plant biochemistry.

The successful candidate will develop a world-class program that will benefit from the unique facilities and resources available in the Institute. Examples of relevant areas include: a) strong background in plant growth/development and adaptation to the environment, including the fledgling field of phenomics, b) developing strategies to significantly redirect carbon allocation from photosynthesis into specific classes of metabolites in plants, and c) identifying and providing novel sources of sustainable, ecologically neutral, plant-derived substances suitable for biofuels and biomaterials.

At Associate-level there must be demonstrated mentoring skills; demonstration of ability to establish an independent research program and an emerging national and international reputation. The Institute (<http://cahnr-cms.wsu.edu/ibc/Pages/default.aspx>) provides a supportive research environment with more than 120 scientists, excellent equipment and facilities, and ready access to specialized techniques in biochemistry, cell biology, phenomics, proteomics, metabolomics and genomics. For more details and to apply, see [www.wsujobs.com](http://www.wsujobs.com), (Search #111600). Candidates should be prepared to submit a letter of application, curriculum vita, a statement of research interests, a description of future research plans and the names and contact information for four professional references. Review of applications will begin **October 15, 2012**.

EEO/AA/ADA.



The Departments of Microbiology and Chemical and Biomolecular Engineering at The Ohio State University invite applications for an Assistant or Associate Professor whose research focuses on Environmental Microbiology and Bioenergy. We seek a Molecular Microbiologist whose research will be directed towards molecular characterization of physiological processes used by microorganisms to produce biofuels or will be

focused on other key environmental issues. Research approaches that include efforts in metabolic engineering and systems biology/synthetic biology are of special interest. This individual will join a vibrant community that includes, in addition to nearly 50 faculty members in the Microbiology (<http://www.microbiology.osu.edu>) and CBE (<http://www.chbmeng.ohio-state.edu/>) departments, researchers at the Office for Energy and the Environment (<http://iee.osu.edu/>), the Center for Energy, Sustainability, and the Environment (<http://oaa.osu.edu/documents/CSEproposal.pdf>), the School of Earth Sciences (<http://www.earthsciences.osu.edu/about.php>), the School of Environment and Natural Resources (<http://senr.osu.edu/>), Battelle Memorial Institute (<http://www.battelle.org/>), and the Environmental Sciences Graduate Program (<http://esgp.osu.edu/>). The expected arrangement will be a 70% appointment in Microbiology and 30% appointment in Chemical and Biomolecular Engineering, but other arrangements may be considered depending on the research interests of the candidate.

Applicants must have a Ph.D. or equivalent degree and relevant postdoctoral research experience. The successful candidate will be expected to establish and maintain an extramurally funded research program and to actively support our strong commitment to excellence in teaching at both the undergraduate and graduate levels.

Applications will be accepted until the position is filled, but priority will be given to applications received by **October 15, 2012**. Application materials, including a letter of intent, curriculum vitae, statement of research and teaching interests, and three letters of recommendation, as well as additional questions about the search, should be sent by e-mail to: [micro.grad@osu.edu](mailto:micro.grad@osu.edu).

*To build a diverse workforce The Ohio State University encourages applications from minorities, veterans, women and individuals with disabilities. Flexible work options are available. Ohio State is an NSF ADVANCE Institution. EEO/AA Employer.*



**Developmental Biology  
Tenure Track  
Faculty Position**

The Department of Developmental Biology ([www.devbio.pitt.edu](http://www.devbio.pitt.edu)) at the University of Pittsburgh School of Medicine is seeking a highly accomplished investigator with strong publication record and significant federal funding for a tenure track Associate Professor position. Candidates should have an innovative research program in the area of developmental neurobiology. There is a strong and vibrant neuroscience research community in the University of Pittsburgh that span a wide range of research interests including, cellular, molecular, systems, cognitive and computational neuroscience. Considerable strength also exists in the areas of neurodegenerative and neuropsychiatric disorders, pain and non-human primate models of normal and abnormal behavior. There are also strong links within our biological and psychological communities that facilitate collaborations across departments and disciplines.

The successful candidate will be housed in new space in the Rangos Research Center of the Children's Hospital of Pittsburgh. The Department has in house SOLiD and Ion Torrent next generation sequencers, wide range of cutting edge imaging modalities for in vivo and live cell imaging, and a stem cell core facility. Multiple other university cores provide infrastructure for mass spectrometry, flow cytometry, gene targeting, and other high-end technical capabilities. The University of Pittsburgh is ranked among the top ten NIH funded research institutions in the US.

Applicants should send CV, a short summary of research interests/future research plans, and names of three referees by **November 30th, 2012** to: [dbsearch@pitt.edu](mailto:dbsearch@pitt.edu).

*The University of Pittsburgh is an  
Equal Opportunity, Affirmative Action Employer.*

## POSITIONS OPEN

### BIOCHEMIST

Williams College the Chemistry Department invites application for a tenure-track position at the **ASSISTANT PROFESSOR** level beginning Fall 2013. A more senior appointment is possible under special circumstances. We are particularly interested in applicants with research interests in experimental biochemistry. Teaching assignments in this position may include courses in biochemistry, biophysical chemistry, upper-level biochemistry courses, introductory chemistry, and courses for non-science majors. A semester teaching assignment normally includes complete responsibility for one course and two laboratory sections, and supervision of student research projects. Candidates should hold a Ph.D. or have completed their dissertation by September 2013 (postdoctoral experience is preferred). The successful candidate must have a strong commitment both to teaching at the undergraduate level and to developing a productive research program. Williams College is a coeducational liberal arts institution located in the Berkshire Hills of western Massachusetts that has built its reputation on outstanding teaching and scholarship and on the academic excellence of its approximately 2,000 students. The Chemistry Department is composed of 12 faculty members and graduates about 30 majors each year; the department has excellent facilities for teaching and research. For more information, see **website: <http://chemistry.williams.edu/>**. The College is committed to building and supporting the diversity of its science majors and seeks an individual who can help us meet these goals. Mail curriculum vitae, undergraduate and graduate transcripts, descriptions of teaching philosophy and research projects for undergraduates, and three letters of recommendation to: **Professor Thomas E. Smith, Chair, Department of Chemistry, 47 Lab Campus Drive, Williams College, Williamstown, MA 01267, by October 2, 2012.** Electronic applications will not be accepted. All offers of employment are contingent upon completion of a background check. Further information is available at **website: <http://dean-faculty.williams.edu/prospective-faculty/background-check-policy/>**.

*Beyond meeting fully its legal obligations for non-discrimination, Williams College is committed to building a diverse and inclusive community where members from all backgrounds can live, learn, and thrive.*

### ASSISTANT PROFESSOR

**in Organic/Organic Chemistry  
Department of Chemistry and Biochemistry  
Utah State University**

The Department of Chemistry and Biochemistry at Utah State University invites applications for a tenure-track position at the Assistant Professor level beginning Fall 2013. Preference will be given to applicants with research interests at the interface of inorganic and organic chemistry, particularly in the areas of organo-transition metal chemistry and catalysis. The successful candidate will have a research program that complements at least one departmental focus area (e.g. catalysis and mechanism, energy and the environment). Applicants must have earned a Ph.D. in Chemistry or a closely related discipline and postdoctoral experience is required. The position requires the development of a nationally recognized, externally funded research program as well as teaching at the undergraduate and graduate levels. The teaching responsibilities will periodically involve lower division courses in general or organic chemistry. Applicants should submit curriculum vitae, a concise description of future research projects, a description of how the research to be pursued complements existing research focus areas in the Department, a description of teaching experience and preferred teaching area(s), and the names and e-mail addresses of three references. Apply online at **website: <http://jobs.usu.edu> (REQ ID 053389)**. Evaluation of applicants will begin October 24; posting will remain open until position is filled. *Utah State University, located in Logan, Utah, is an Equal Opportunity/Affirmative Action Employer committed to assembling a diverse faculty. Women and members of minority groups are strongly encouraged to apply.*

## POSITIONS OPEN

### ASSISTANT PROFESSOR

**Chemical Biology  
Utah State University**

The Department of Chemistry and Biochemistry at Utah State University (USU) invites applications for a tenure-track position at the Assistant Professor level in the area of Chemical Biology beginning Fall 2013. The successful candidate will have a research program that complements at least one departmental focus area (i.e., macromolecular structure and function and/or eukaryotic biochemistry), the technical infrastructure within the department, and should also allow the candidate to interact with researchers in the biological sciences from other USU departments and colleges. Applicants must have earned a Ph.D. in Chemistry, Biochemistry, Biology, or a related field; postdoctoral experience is required. The position requires the development of an externally funded research program as well as teaching at the undergraduate and graduate levels. Applicants should submit curriculum vitae, a concise description of future research projects, a description of how the research to be pursued complements existing research focus areas and technical infrastructure in the Department, a description of teaching experience and preferred teaching area(s), and the names and e-mail addresses of three references. Apply online at **website: <http://jobs.usu.edu> (REQ ID 053398)**. Evaluation of applicants will begin October 24; posting will remain open until position is filled. For more information, please visit our **website: <http://www.usu.edu/science/html/chemical-biology>**.

*Utah State University, located in Logan, Utah, is an Equal Opportunity/Affirmative Action Employer committed to assembling a diverse faculty. Women and members of minority groups are strongly encouraged to apply.*

### EVOLUTIONARY ECOLOGIST

**Assistant Professor  
Tenure-track**

The Department of Zoology at Oklahoma State University (OSU), **website: <http://zoology.okstate.edu>** invites applications for an Assistant Professor in evolutionary ecology. We seek applicants whose core research includes genomic, epigenetic, computational, or behavioral approaches to integrate biological processes across multiple levels of organization. Applicants should have a Ph.D., postdoctoral experience, teaching experience, and success in obtaining extramural funding. Responsibilities include establishing an extramurally funded research program, mentoring M.S. and Ph.D. students, and teaching at the undergraduate and graduate levels. To apply (1) send a single PDF file composed of a cover letter, curriculum vitae, and statements of research interests and teaching philosophy, and (2) arrange to have three letters of recommendation sent to the search committee chair, **Dr. Meredith Hamilton**, at **e-mail: [zoologysearch@okstate.edu](mailto:zoologysearch@okstate.edu)**. Application review begins October 15, 2012, with employment beginning August 16, 2013. Filling of this position is contingent upon funding availability. *Oklahoma State University is an Affirmative Action/Equal Employment Opportunity/E:Verify Employer committed to diversity. OSU-Stillwater is a tobacco-free campus.*

### ASSISTANT PROFESSOR-ALL AREAS

**Princeton University  
Department of Chemistry**

The Department of Chemistry at Princeton University invites applications for a tenure-track Assistant Professor position in all areas of chemistry. Candidates should have a strong commitment to research and to teaching at the undergraduate and graduate levels, and are expected to have completed the Ph.D. in chemistry or a related field at the time of appointment. Applicants should submit a description of research interests, curriculum vitae, a list of publications, and contact information for three references online at **website: <http://jobs.princeton.edu/applicants/Central?quickFind=62756>**. The search committee will begin review of applications on October 17, 2012 and will continue until the position is filled.

*Princeton University is an Equal Opportunity Employer and complies with applicable EEO and Affirmative Action regulations.*

## POSITIONS OPEN

### BIOLOGICAL SCIENCES

Tenure-track **ASSISTANT PROFESSOR**. Ph.D. in a biological science, completed by July 31, 2013; broad training and/or experience in biological sciences; experience in college teaching required. Preference given to applicants with experience working with diverse groups, and a willingness to help the department develop innovative teaching strategies. The Department of Biological Sciences at California State University, Sacramento has a focus on teaching, scholarship, and service. Faculty members are expected to achieve excellence in classroom teaching. Faculty members are also expected to engage in scholarship, university service, and community service to be retained and earn tenure and promotion. Need exists in several areas of the curriculum: genomics/genetics, physiology, anatomy, microbiology, cell/molecular biology, forensic biology, and introductory biology for majors. Submit current curriculum vitae; all transcripts; e-mail addresses and telephone numbers of three references; statements of teaching and scholarly interests; and three recent letters of recommendation to: **Jennifer Lundmark, Chair, Biological Sciences, California State University, Sacramento, CA 95819-6077. Website: <http://www.csus.edu/bios/>**. To ensure full consideration, all application materials should be received by October 15, 2012; position open until filled. For detailed position information **website: <http://www.csus.edu/hr/faculty/NSM/index.htm>**. *Affirmative Action/Equal Employment Opportunity. Clery Act statistics available.*

### ORGANIC CHEMISTRY

The Department of Chemistry at the University of Michigan invites applications for a tenure-track position at any rank with a proposed start date of September 1, 2013. Candidates with research interests in the area of organic chemistry (including synthesis, methods development, physical organic, organometallic, bioorganic, and organic materials chemistry) will be given priority. This will be a University-year appointment (nine-month academic salary with summer salary supported by research funds). Candidates are expected to develop an internationally recognized program of scholarly research and to excel in teaching at undergraduate and graduate levels.

Detailed information regarding the electronic application process and required materials is available online at **website: <https://www.chem.lsa.umich.edu/chem/facultyrecruit/>**. Review of applications will begin on October 1, 2012.

Information about the Chemistry Department is available on **website: <http://www.umich.edu/~michchem>**. Questions about the application process should be sent to **e-mail: [chemfacrecruit@umich.edu](mailto:chemfacrecruit@umich.edu)**.

*Women and minorities are encouraged to apply. The University of Michigan is supportive of the needs of dual career couples and is an Equal Opportunity/Affirmative Action Employer.*

### FACULTY SEARCH

The Department of Chemistry at the University of Michigan invites applications for an anticipated tenure-track position at any rank in any subdiscipline of chemistry (including analytical, chemical biology, education, inorganic, materials, organic and physical) with a proposed start date of September 1, 2013. This will be a University-year appointment (nine-month academic salary with summer salary supported by research funds). Candidates are expected to develop an internationally recognized program of scholarly research and to excel in teaching at undergraduate and graduate levels.

Detailed information regarding the electronic application process and required materials is available online at **website: <https://www.chem.lsa.umich.edu/chem/facultyrecruit/index.html>**.

Review of applications will begin on October 1, 2012.

Information about the Chemistry Department is available on the **website: <http://www.umich.edu/~michchem>**. Questions about the application process should be sent to **e-mail: [chemfacrecruit@umich.edu](mailto:chemfacrecruit@umich.edu)**.

*Women and minorities are encouraged to apply. The University of Michigan is supportive of the needs of dual career couples and is an Equal Opportunity/Affirmative Action Employer.*





The Department of Biomedical Engineering at Carnegie Mellon University, undergoing rapid expansion, seeks the appointment of tenure-track faculty members at all levels. A successful candidate is expected to build a vigorous research program

that meshes with and enhances the extensive research network as described on <http://www.bme.cmu.edu>, particularly in the areas of cellular and cardiovascular biomechanics, biomedical imaging and signal processing, bioMEMS, and smart medical devices and materials. The College of Engineering at Carnegie Mellon is ranked consistently among the top 10 engineering schools by USNWR. Faculty members of the Department enjoy a strong university-wide collaborative culture, excellent research support, modest teaching load, outstanding students, and comprehensive benefits.

Applicants should send CV, three letters of recommendation, and vision statements on research and teaching to [bme-search@andrew.cmu.edu](mailto:bme-search@andrew.cmu.edu). Applications will be reviewed on a rolling basis until February 2013.

*Carnegie Mellon University, an Equal Opportunity/Affirmative Action Employer, strongly encourages applications from women, under-represented minorities, individuals with disabilities, and individuals from disadvantaged backgrounds.*



## Positions Available in Genome Sciences

The Penn State University College of Medicine, located in Hershey, PA, seeks qualified applicants for the positions in Genome Sciences described below. Review of applications for both positions will begin immediately and continue until filled. Salary will be commensurate with the candidate's experience and credentials. Candidates should submit a letter of application including statement of current and future research interests, curriculum vitae, and names and contact information of three references. Electronic applications are preferred and should be sent to [dpague@phs.psu.edu](mailto:dpague@phs.psu.edu). Please note position you are applying for in your cover letter. Applications also may be submitted via mail to: **Genome Sciences Search Committee c/o Diane Pague, Department of Public Health Sciences; 600 Centerview Drive, Suite 2200; Hershey, PA 17033.**

### Assistant/ Associate Professor in Bioinformatics or Statistical Genomics

The Penn State Hershey Institute for Personalized Medicine (IPM) seeks applicants in bioinformatics and statistical genomics. The IPM is charged with defining genetic or other molecular biomarkers that influence disease risk and treatment outcomes and that can be applied to tailor treatment of individual patients. Successful applicants are expected to develop independent research programs that exploit the unique resources of the Institute and advance the ability of investigators to correlate disease and treatment outcomes with appropriate biomarkers. Successful candidates will be appointed to tenure-track Assistant or Associate Professor positions in one of the affiliated departments.

Qualifications include a PhD or equivalent degree in one or more of the areas listed below with relevant postdoctoral research training and a record of excellence in research.

- 1) Bioinformatics, especially with respect to high-throughput data extraction, analysis and modeling;
- 2) Statistical genomics with a focus on correlation of genetic or other biomarkers with disease susceptibilities and outcomes;
- 3) Computational biology with expertise in development of tools and algorithms for interrogating and exploiting large data sets.

### Technical Director, Genome Sciences Core Facility

The Genome Sciences Facility seeks faculty applicants for a Technical Director. The Genome Sciences Core provides a range of genetic, epigenetic, and transcriptomic technologies to researchers from throughout Penn State University. Qualifications include a PhD in a relevant field and in-depth, first-hand experience in high content molecular biological analyses, including next-generation sequencing, qPCR, and microarrays. A focus of the position will be next-generation sequencing for genomic, epigenomic, and transcriptomic studies. In addition to overseeing day-to-day operations of the facility, the successful candidate will collaborate with a wide variety of biomedical researchers to aid in successful completion of their research projects.

*The Pennsylvania State University College of Medicine is an Equal Opportunity, Affirmative Action Employer. Women and minority candidates are especially encouraged to apply. For your health, we are a non-smoking campus.*



Department of  
Molecular  
Microbiology

## Faculty Positions in Molecular Microbiology Washington University School of Medicine in St. Louis

We are seeking outstanding candidates for three **TENURE-TRACK** faculty positions at the Assistant, Associate, or Full Professor level in the Department of Molecular Microbiology at Washington University in St. Louis School of Medicine. Ideal applicants will be creative scientists pursuing fundamental aspects of microbial pathogenesis using innovative and interdisciplinary combinations of genomics, genetics, cell biology, computational biology and biochemistry in viral, prokaryotic or eukaryotic microbes. We especially encourage applicants with bold new perspectives and 'outside the box' approaches. One of the new positions will be associated with the Center for Women's Infectious Disease Research (cWIDR) (<http://cwidr.wustl.edu/>). We welcome applications from members of groups that are typically under-represented in science. Washington University offers an intellectually exciting, collegial, and supportive environment with robust graduate and post-doctoral programs and extensive opportunities for interdepartmental collaboration. Resources include outstanding core facilities for genomics, high throughput screening, imaging, and high performance cluster computing, and BSL3 space including animal facilities. Additional information can be found at [www.microbiology.wustl.edu](http://www.microbiology.wustl.edu). Applicants should be committed to the teaching of graduate and professional students and the establishment of a vigorous, cutting-edge, externally funded research program. Requirements include a Ph.D. in an appropriate discipline, postdoctoral training, and evidence of scholarly publications. Applicants should send a single PDF document containing a Curriculum Vitae, up to 3 reprints, and a 2-3 page description of current and planned research interests to [microsearch2012@borcim.wustl.edu](mailto:microsearch2012@borcim.wustl.edu). Three letters of recommendation should be sent separately. Complete applications will be evaluated on a rolling basis beginning October 1, 2012. All materials must be received by **November 15, 2012**.

*WUSM is an Equal Opportunity/Affirmative Action Employer. Women and minorities are especially encouraged to apply.*



## Assistant Rice Cropping Systems Cooperative Extension Specialist Department of Plant Sciences

Assistant Specialist in Cooperative Extension. An 11-month, career-track extension position with 100% Cooperative Extension responsibilities located in the UC Davis Department of Plant Sciences. Candidate will provide statewide research and extension leadership in rice production systems. The research and extension program will address the need for balancing multiple management goals, including optimizing rice productivity by addressing agronomic issues such as soil fertility, nutrient management and cycling, water use efficiency and quality, carbon sequestration, and overseeing the statewide variety evaluation program. The candidate is expected to develop a nationally-recognized program, secure extramural funding, and publish research results in appropriate refereed journals and reports. Candidate will interact with diverse clientele groups, provide training and advising to appropriate groups, and develop an affirmative action program. Candidate will have the opportunity to direct undergraduate and graduate research. Requirements include: a Ph.D. in agronomy, agricultural production, plant sciences, agroecology, or a closely related field with an emphasis in applied cropping systems; leadership ability, management and communication skills; ability to conduct independent research must be demonstrated.

Candidates should begin the application process by registering online at <http://recruitments.plantsciences.ucdavis.edu/>. Please include statements of research and extension interests, curriculum vitae, publication list, copies of 3 of your most important research publications, copies of undergraduate and graduate transcripts (if within 5 years of either degree), and the names, e-mail addresses, and telephone numbers of at least five professional references. For administrative questions regarding the application process, please email [Mrs. Cindy Ramirez, cmsalazar@ucdavis.edu](mailto:Mrs. Cindy Ramirez, cmsalazar@ucdavis.edu). Review of the applications for this position will begin **December 1, 2012**. The position will remain open until filled.



## POSITIONS OPEN

### FACULTY POSITIONS Virology and Bacterial Pathogenesis (Bacterial/Host Interactions)

The Microbiology department at UT Southwestern Medical Center at Dallas is seeking new faculty, at the **ASSISTANT PROFESSOR** (tenure track) level, in virology and bacterial pathogenesis (including bacterial/host interactions). This will be a rolling search until positions are filled. Appointees will be expected to develop front-rank, competitive, independent research programs on medically relevant pathogens. For virology, some preference will be given to candidates working on RNA viruses and/or viral pathogenesis. The appointees will contribute to the teaching of medical and graduate students. Attractive startup packages, including a competitive salary and generous laboratory space in a new building, are available to conduct research in an expanding, dynamic environment. Candidates also will be considered for UT Southwestern's \$1.2M Endowed Scholars (startup) Program. Candidates should have a Ph.D. and/or M.D. degree with at least three to four years of postdoctoral experience and an exceptional publication record. Candidates should send a cover letter, curriculum vitae, contact information for three letters of recommendation, and a brief summary of future research to either e-mail: [virologysearchcommittee@utsouthwestern.edu](mailto:virologysearchcommittee@utsouthwestern.edu) or [bacterialpathogenesissearchcommittee@utsouthwestern.edu](mailto:bacterialpathogenesissearchcommittee@utsouthwestern.edu). UT Southwestern is an Equal Opportunity/Affirmative Action Employer.

### ASSISTANT PROFESSORSHIP in Neurobiology Western Washington University

The Biology Department at Western Washington University (WWU), a regional comprehensive university located between Seattle and Vancouver B.C., invites applications for a tenure-track, assistant professor position, beginning September 2013. We seek an individual committed to undergraduate and M.S. education who will establish a vigorous research program that involves students. Ph.D., postdoctoral experience in cell and molecular neurobiology, and potential to establish a research program in cell and molecular neurobiology in a non-mammalian system required. Applicants who can contribute to our Behavioral Neurosciences program are of particular interest. The applicant must provide evidence of the ability to teach introductory cell and molecular biology and advanced courses in neurobiology, cell biology, or genetics. Review begins October 22, 2012. See full position announcement, including all required and preferred qualifications, at [website: http://biol.www.wu.edu/biology/](http://biol.www.wu.edu/biology/). For application information and instructions, go to the WWU Employment [website: http://www.wu.edu/jobs](http://www.wu.edu/jobs). Affirmative Action/Equal Opportunity Employer.

### FACULTY POSITION in Cell Biology/Development/Neurobiology

The Department of Zoology, University of Wisconsin-Madison, invites applications for a tenure-track position at the **ASSISTANT PROFESSOR** level, beginning August 2013. Requirements include a Ph.D. and postdoctoral experience in cell biology/development/neurobiology, or related area and demonstrated research accomplishments. Teaching will include courses at the undergraduate and graduate level. For additional information, see our departmental [website: http://www.wisc.edu/zoology](http://www.wisc.edu/zoology).

Please send a single PDF file containing your cover letter, complete curriculum vitae, statement of research and teaching interests, and full contact information for three references to the CDNB Search Committee via e-mail: [mnowicki@wisc.edu](mailto:mnowicki@wisc.edu). Questions should be directed to e-mail: [aostrett@wisc.edu](mailto:aostrett@wisc.edu), Telephone: 608-262-2172, fax: 608-262-9083. Deadline: For full consideration, apply by December 1, 2012. Only applications submitted by e-mail will be accepted.

An Equal Opportunity/Affirmative Action Employer. Women and minorities are encouraged to apply. A criminal background check will be required prior to appointment. Unless confidentiality is requested in writing information regarding applicants must be released upon request. Finalists cannot be guaranteed confidentiality.

## POSITIONS OPEN

### ASSISTANT PROFESSOR OF CHEMISTRY Berry College

The Department of Chemistry at Berry College, an ACS-approved program, invites applications for a tenure-track position as Assistant Professor to start August 2013. Primary responsibilities include teaching organic chemistry, biochemistry and associated laboratories. The successful applicant will establish a productive research program involving undergraduate students in the area of bioorganic chemistry. In addition to a commitment to excellence in teaching and scholarship, candidates should possess a strong interest in service and mentoring students in a residential liberal arts environment. A Ph.D. degree in either Chemistry or Biochemistry is required; postdoctoral research experience is desired. Send a letter of application, curriculum vitae, copies of undergraduate and graduate transcripts, statement of teaching philosophy, and summary of research plans (including equipment needs), and arrange to have three letters of recommendation sent to: **Dr. Gary Breton; Department of Chemistry; P.O. Box 495016; Mount Berry, GA 30149**. Review of applications will begin October 1, 2012. Please visit us online for information on the department, [website: http://www.berry.edu/academics/science/chemistry/](http://www.berry.edu/academics/science/chemistry/). Persons filling out an application for employment with Berry College may be required to submit a full national background check. Located on more than 26,000 acres in north-west Georgia in a setting of great natural beauty, Berry College is a selective liberal arts college with an enrollment of 2,000 students and an emphasis on academic excellence, practical work experience, and an interdenominational religion-in-life program. Equal Opportunity Employer.

The Dauphin Island Sea Lab (DISL) invites applications for a faculty position in Coastal Benthic Ecology. We seek an individual who uses observational and experimental approaches to study benthic systems (e.g., submerged aquatic vegetation, coral reefs, wetlands, meiofaunal communities), scaling from population to ecosystem levels and who can bring skills that would complement the existing faculty. Some examples of skill sets sought are quantitative modeling, climate change research, and hydrodynamic-biological coupling, but other sets will also be entertained. We expect to hire at the level of Senior Marine Scientist I (equivalent to **ASSISTANT PROFESSOR**); exceptional candidates may be considered at a higher rank. Duties include establishing and maintaining a productive research program, teaching an undergraduate summer course in Marine Ecology, one graduate course per year and advising graduate students. Competitive startup funding is available. A Ph.D. must be completed prior to the start date. postdoctoral experience is highly preferred. For more information on DISL, see [website: http://www.disl.org](http://www.disl.org). Applicants should send curriculum vitae, a brief statement of research interests and teaching philosophy, two to three selected reprints, and the names and contact information (including e-mail addresses) of three references to the Senior Marine Scientist Search Committee (e-mail: [smssearch@disl.org](mailto:smssearch@disl.org)). Applications can also be sent through regular mail to: **Just Cebrian, Chair of Marine Science Search Committee, DISL, 101 Bienville Boulevard, Dauphin Island, AL 36528**. Review of applications will begin December 1, 2012 and will continue until the positions are filled. DISL is an Equal Opportunity Employer/Affirmative Action Employer, including Minorities/Females/Persons with Disabilities.

## POSITIONS OPEN

### YALE UNIVERSITY WEST CAMPUS

The Chemical Biology and Cancer Biology Institutes at Yale West Campus invite applications for positions at the **ASSISTANT, ASSOCIATE, or FULL PROFESSOR** level to commence 1 July 2013. Faculty associated with the West Campus hold primary appointments in any of several life science or physical science departments within the Faculty of Arts and Sciences, the School of Engineering and Applied Science, and the Yale School of Medicine. At this time, we seek candidates whose research interests and accomplishments fall in the area of mass spectrometry with a focus on proteomics and/or metabolomics. Successful candidates will be creative teacher-scholars with reputations for outstanding research at the combined interface of engineering, chemistry, biology, and/or medicine, and must possess a Ph.D. in a relevant discipline. Applicants should create a profile at [website: https://academicjobsonline.org/ajob/jobs/1730](https://academicjobsonline.org/ajob/jobs/1730) and upload a statement of research plans, curriculum vitae, and up to five reprints of published work(s). Applicants for positions at the Assistant Professor rank should also arrange for three references to upload their letters of recommendation. For further information, contact **Jessica Sorensen** at e-mail: [jessica.sorensen@yale.edu](mailto:jessica.sorensen@yale.edu) or: **PO Box 27392, West Haven, CT 06516-7390**.

The review of applications will begin on 15 October 2012 and proceed until suitable candidates are identified.

Yale University is an Affirmative Action/Equal Opportunity Employer. Yale values diversity among its faculty, students, and staff and strongly encourages applications from women and underrepresented minorities.

### MOLECULAR BIOLOGIST

#### Assistant Professor of Biology Amherst College

The Department of Biology at Amherst College seeks to fill a tenure-track position at the Assistant Professor level in molecular biology, to begin July 2013.

The successful candidate will mount an active research program that involves undergraduate students. Teaching duties include participation in lecture courses with laboratories in biochemistry, in molecular genetics, and in a team-taught introductory course in molecular and cellular biology. A completed Ph.D. is required and postdoctoral experience is expected.

Candidates should submit electronically a cover letter, curriculum vitae, separate research and teaching statements, and the names and e-mail addresses of three individuals to whom we may write to solicit recommendations. These materials should be submitted to [website: https://jobs.amherst.edu/view/opportunity/id/445](https://jobs.amherst.edu/view/opportunity/id/445). Teaching statements should explicitly address the candidate's approaches to teaching biochemistry and molecular genetics. Review of applications will begin October 1, 2012, and will continue until the position has been filled.

Amherst College is a private undergraduate liberal arts college for men and women, with 1,700 students and a teaching faculty of 200. Located in the Connecticut River Valley of western Massachusetts, Amherst participates with Hampshire, Mount Holyoke and Smith Colleges and the University of Massachusetts in the Five College Consortium. Amherst College is an Equal Opportunity Employer and encourages women, persons of color, and persons with disabilities to apply.

Stop searching for a job;  
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customized job alerts.  
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# Yale

## Faculty Position at Yale University Department of Molecular, Cellular and Developmental Biology

The Department of Molecular, Cellular and Developmental Biology at Yale University invites applications for a faculty appointment as an assistant professor from individuals working on any area of plant biology. The Department encourages applications from candidates using any experimental approach, including molecular, genetic, biochemical, or genomic/proteomic approaches, to investigate outstanding questions in modern plant biology at the organismal, cellular or molecular level. We expect successful candidates to develop active research groups, be interactive members of the faculty and participate in interdisciplinary research and training. Successful candidates should demonstrate communication skills commensurate with excellence in teaching at both the undergraduate and graduate levels.

Application review will begin on **December 15, 2012**. Submit an application, a curriculum vitae and a description of research interests on line to <https://academicjobsonline.org/ajoyale>. Request at least three individuals submit letters of recommendation on your behalf to <https://academicjobsonline.org/ajoyale>. For questions, please e-mail [mcd.b.plantsearch@yale.edu](mailto:mcd.b.plantsearch@yale.edu).

*Yale University is an Affirmative Action/Equal Opportunity Employer. Women and members of underrepresented minority groups are especially encouraged to apply.*

# KU THE UNIVERSITY OF KANSAS

## Assistant or Associate Professor in Microbiology

The Department of Molecular Biosciences at the University of Kansas invites outstanding candidates to apply for a tenure-track faculty position at the Assistant or Associate Professor level in **Microbiology**. Applicants are sought with demonstrated expertise in Microbiology and human infectious diseases. The Department of Molecular Biosciences provides a highly interactive and exciting multi-disciplinary research environment that includes successful and active researchers in Microbiology, Biochemistry, Bioinformatics, Cell and Developmental Biology, and Genetics (<http://www.molecularbiosciences.ku.edu/>). As such, Microbiologists who combine the study of human-associated pathogenic microbes with state-of-the-art approaches in these areas are of interest. The University of Kansas has many excellent core facilities including the Animal Care Unit, and laboratories in Genomics, High-Throughput Screening, Microscopy and Analytical Imaging, and Protein Structure, to facilitate research in these areas. Additionally, the University of Kansas has a demonstrated strength in drug discovery and development and a trans-disciplinary, inter-campus Program in Microbiology (<http://www.micro.ku.edu/>).

Applicants at the Assistant Professor level are expected to demonstrate potential for establishing an independent, externally funded research program, and those at the Associate level are expected to have an established and currently funded program with demonstrated potential for continuance. The successful candidate will also be expected to direct graduate student research and participate in the department undergraduate and/or graduate teaching missions.

The University of Kansas is especially interested in hiring faculty members who can contribute to four key campus-wide strategic initiatives: (1) Sustaining the Planet, Powering the World; (2) Promoting Well-Being, Finding Cures; (3) Building Communities, Expanding Opportunities; and (4) Harnessing Information, Multiplying Knowledge. For more information, see <http://www.provost.ku.edu/planning/themes/>.

Initial review of applications will begin **December 3<sup>rd</sup>, 2012** and continue as long as needed to identify a qualified pool. Appointment is expected to begin as early as August 18<sup>th</sup>, 2013. Applicants must have a Ph.D. in Microbiology or related discipline plus applicable postdoctoral or faculty experience. Women and minorities are highly encouraged to apply. To apply, go to <https://jobs.ku.edu> and search for position **00002241** and upload (1) a letter of application, (2) *curriculum vitae*, and statements of (3) current/future research and (4) teaching interests/philosophy. Please include a list of at least three professional references for which letters of recommendation can be requested. Queries regarding this position can be addressed to Scott Hefty, Search Committee Chair, at [pshefty@ku.edu](mailto:pshefty@ku.edu).

*Equal Opportunity Employer M/F/D/V.*



The **Georgia Institute of Technology** is one of the top ranked educational/research institutions in the country and ranked as one of the best places to work. As part of significant growth in the biological sciences, the **School of Biology** is seeking applications for the following tenure-track positions:

**Two positions in ecology** for empiricists applying molecular and/or field approaches to understand fundamental ecological and evolutionary questions (including, but not limited to, chemical signaling, ecological genetics, and/or responses to environmental perturbation and biotic threats). Candidates will be favored whose research integrates well with existing strengths and ongoing growth in ecosystem processes and environmental health, regulation of phenotypic plasticity and development, aquatic chemical ecology, genetics and mechanisms of microbial community interactions, and biologically inspired design ([www.biology.gatech.edu](http://www.biology.gatech.edu)). These positions will be filled at the assistant/associate level but outstanding senior candidates with exceptional records are encouraged to apply.

**Experimental integrative or structural biology, endowed, full professor.** We are seeking an outstanding senior scientist who is using approaches designed to provide a temporal, structural and spatial understanding of cellular biomolecular processes and the dynamics of cellular organization and function, the chemical biology of cells, and protein interactomics. A generous startup package and laboratory space will be provided.

Georgia Tech is an interdisciplinary environment where faculty are strongly encouraged to interact with engineering, computing, and other science faculty. Candidates can submit an application online at <http://searches.biology.gatech.edu>, including a letter of application, curriculum vitae, statement of research interests and plans, and contact information for five references. Review of applications begins **October 1, 2012** and will continue until positions are filled.

*Georgia Tech is a unit of the University System of Georgia and an Affirmative Action/Equal Opportunity Employer and requires compliance with Immigration Control Reform Act of 1986.*

**GEORGIA INSTITUTE OF TECHNOLOGY**



## Bioinformatics/Computational Biology

The Center for Bioinformatics (Bioinformatics Program) and the Department of Molecular Biosciences invite applications for an assistant professor tenure-track faculty position to begin as early as August 18, 2013. The interdisciplinary Center for Bioinformatics ([www.bioinformatics.ku.edu](http://www.bioinformatics.ku.edu)) complements existing strengths in the Department of Molecular Biosciences ([www.molecularbiosciences.ku.edu](http://www.molecularbiosciences.ku.edu)), including structural biology, computational chemistry, proteomics, and developmental/molecular genetics, as well as strengths in drug design and information technology in the Schools of Pharmacy and Engineering. The Center fosters international activities in Bioinformatics and combines outstanding research and a Ph.D. program.

**Required Qualifications:** Ph.D. and postdoctoral experience in a discipline related to Bioinformatics is expected by the start date of the appointment; potential for excellence in research in Bioinformatics; commitment to teaching life sciences courses; and strong record of research accomplishments in at least one of the following areas: modeling of macromolecular structure and interactions, modeling of protein networks, genomics, and systems biology.

For the full position announcement and to apply online, go to: <https://jobs.ku.edu> and search for position **00002878**. Submit a CV, letter of application, statement of past and future research, statement of teaching interests and philosophy, and a list of at least three references who may be contacted via telephone or e-mail. Initial review of applications begins **October 15, 2012** and will continue as long as needed to identify a qualified pool. Direct inquiries to **Dr. Ilya Vakser** ([vakser@ku.edu](mailto:vakser@ku.edu)).

The University of Kansas is especially interested in hiring faculty members who can contribute to four key campus-wide strategic initiatives: (1) Sustaining the Planet, Powering the World; (2) Promoting Well-Being, Finding Cures; (3) Harnessing Information, Multiplying Knowledge; and (4) Building Communities, Expanding Opportunities. See [www.provost.ku.edu/planning/themes/](http://www.provost.ku.edu/planning/themes/) for more information.

*Equal Opportunity Employer M/F/D/V.*





## Faculty Positions

The Center for Immunology and Microbial Disease at Albany Medical College invites applications for multiple tenure-track Assistant Professor, Associate Professor, and full Professor positions from individuals who have a doctoral degree, postdoctoral experience, and demonstrated research productivity. Applicants for a senior faculty position should have an internationally-recognized research program in microbiology and/or host-pathogen interactions. The basic science departments at Albany Medical College are organized as interdisciplinary research centers and the Center for Immunology and Microbial Disease has a focus on microbial pathogenesis and immune defense, particularly as related to biothreat agents and emerging infections. Our faculty comprises a highly collaborative research group that this year received \$12.2M in NIH funding, ranking it within the top half of all Microbiology and Immunology programs in the country. The successful candidates will receive attractive start-up packages and will have an opportunity to lead a focus group in new laboratory space, with access to all departmental core facilities including the Center's fully-staffed ABSL-3/BSL-3. We have established a close relationship with the New York State Department of Health Wadsworth Laboratories, providing a diverse environment that is rich in infectious disease expertise. Albany Medical College is located in a mid-sized city within the upstate New York Capital Region, and has easy access to Boston, New York City, and the Adirondack Mountains.

Applicants should send their curriculum vitae, a statement of research plans, and contact information for three references to:

**Faculty Search Committee**  
**Center for Immunology and Microbial Disease**  
**Albany Medical College**  
**47 New Scotland Avenue, MC-151**  
**Albany, NY 12208**

For further information about the Center, visit:  
[www.amc.edu/Research/imd](http://www.amc.edu/Research/imd)

*An Equal Opportunity/Affirmative Action Employer.  
 Women and minorities are encouraged to apply.*



**Georgia Institute  
 of Technology**

## Hightower Endowed Chair in Biopolymers

The School of Materials Science and Engineering at the Georgia Institute of Technology invites applications and nominations for the Hightower Chair in Biopolymers. This senior position will serve as a focal point within the School and the Institute for research and teaching in the field of biopolymers, while working to broaden interactions in polymer science, bio-materials and polymeric materials having a biological origin or function. Candidates with interests in the theory, design, synthesis, processing, characterization, and applications of biopolymers are especially encouraged to apply. There are numerous opportunities for campus-wide interactions in the various units of the Colleges of Engineering and Science, including the School of Applied Physiology and the Department of Biomedical Engineering. Further interactions are envisioned with the Parker H. Petit Institute for Bioengineering and Bioscience (IBB), the Strategic Energy Institute (SEI), and the Institute for Electronics and Nanotechnology (IEN). The successful candidate should have a history of establishing outstanding research programs, a demonstrated interest in fostering collaboration, and a commitment to high-quality teaching with the opportunity to develop courses and academic programming in biopolymers. The metropolitan Atlanta region provides much opportunity for local cooperation in medical research and development, along with potential entrepreneurial opportunities through the Institute's (IC)<sup>3</sup> program.

Candidates should submit an application letter describing their vision for the position, a curriculum vitae, and names (and contact information) for five references to [www.mse.gatech.edu/Hightower](http://www.mse.gatech.edu/Hightower). The application review process will begin immediately and will continue until the position is filled. Enquiries may be made to chair of the search committee at [anselm.griffin@mse.gatech.edu](mailto:anselm.griffin@mse.gatech.edu). All enquiries and applications will be treated as confidential.

*Georgia Institute of Technology is an Equal Opportunity/Affirmative Action Employer. Applications and nominations from female and minority candidates are encouraged.*

## THE LINDA AND JACK GILL CENTER FOR BIOMOLECULAR SCIENCE INDIANA UNIVERSITY, BLOOMINGTON, IN

### ENDOWED PROFESSORSHIP IN CELLULAR/ MOLECULAR NEUROSCIENCE

Indiana University – Bloomington and The Linda and Jack Gill Center for Biomolecular Science seek an outstanding senior-level molecular or cellular neuroscientist to join the Gill Center ([www.indiana.edu/~gillctr](http://www.indiana.edu/~gillctr)) as one of five endowed chairs. This position offers an attractive salary and start-up package, a generous annual endowment, and access to substantial core facilities. The Gill Center Laboratories are housed in a new research building. We specifically seek an individual with a record of outstanding research contributions, proven ability to secure sustained extramural funding, expertise in state-of-the art molecular and cellular neuroscience techniques, and demonstrated leadership in their chosen field. A PhD and/or MD in a relevant discipline is required. The Gill Center was established by a generous gift from Linda and Jack Gill with a mission to address important neuroscience questions using cutting edge technology. Questions about the position can be directed to the director of the Gill Center, Ken Mackie ([kmackie@indiana.edu](mailto:kmackie@indiana.edu)). Applicants should electronically submit dossiers, including a curriculum vita, a statement of research accomplishments and future plans, representative publications, and the names of three references to Misty Theodore ([gillctr@indiana.edu](mailto:gillctr@indiana.edu)).

*Applications will be reviewed until the position is filled. Indiana University is an Affirmative Action Employer. Applications from women and minority candidates are especially encouraged.*



**INDIANA UNIVERSITY**  
 BLOOMINGTON

## Faculty Position in Molecular Pathogenesis Department of Biological Sciences Purdue University

The Department of Biological Sciences, Purdue University, invites applicants for a tenure-track faculty position in the area of Molecular Pathogenesis. Potential areas of research in bacterial or viral systems include: • Host-microbe interactions • Structural basis and mechanisms of pathogenesis • Systems biology of pathogenic organisms • Trafficking of intracellular pathogens

Applicants must have a Ph.D. or equivalent in an appropriate discipline such as microbiology, cell biology, or structural biology and at least 2 years of postdoctoral experience. We expect to fill this academic year appointment at the Assistant Professor level. The successful applicant is expected to conduct research to address fundamental questions in the areas listed above; teach undergraduate and graduate students; and participate in ongoing programs in the Department of Biological Sciences.

The Department has over 50 faculty members conducting research in a wide range of fields including microbiology/virology, structural biology, molecular/cell biology, plant biology, bioinformatics, evolutionary biology, and ecology. Further information about the Department is available at <http://www.bio.purdue.edu/>. The successful candidate will have opportunities to interact with microbiologists across the University, including colleagues in Discovery Park's Bindley Bioscience Center. Instrumentation for systems level analyses and biological image analysis is available at the Bindley Bioscience Center and Birk Nanotechnology Center. Purdue University is expanding Life Sciences research with new facilities in the Jischke Hall of Biomedical Engineering and the Hockmeyer Hall of Structural Biology.

Applications must be submitted electronically to <https://hiring.science.purdue.edu> as a single PDF file that includes a detailed curriculum vitae, names and addresses of three referees, a 2 - 3 page summary of research interests, and a one-page teaching statement. Inquiries should be directed to **Microbiology Search Committee, Department of Biological Sciences, Purdue University, 915 W. State St., West Lafayette, IN 47907-2054** or emailed to [search@bio.purdue.edu](mailto:search@bio.purdue.edu). Review of applications will begin **October 15, 2012** and continue until the position is filled. A background check will be required for employment in this position.

*Purdue University is an Equal Opportunity/Equal Access/Affirmative Action Employer fully committed to achieving a diverse workforce.*





## ASSISTANT PROFESSOR

The Department of Neuroscience at the University of Texas Southwestern Medical Center, under the leadership of Dr. Joseph Takahashi, invites applications at the Assistant Professor level for a tenure-track Faculty position in the broadly defined areas of neurogenetics, electrophysiology and imaging. We seek outstanding scientists addressing molecular and genetic mechanisms underlying behavior, neural circuits and related neurological disorders. Our emphasis is on individuals using forward genetic approaches to understand the nervous system and behavior. Individuals using advanced functional approaches to study neural circuits are also particularly encouraged to apply. Scientists within the Department of Neuroscience participate in a vibrant, interdisciplinary, interdepartmental, and highly collaborative research community within the University, and enjoy access to state-of-art research cores in imaging, mouse MRI imaging, metabolic phenotyping, behavioral phenotyping, protein chemistry, structural biology, genomics, genetics and transgenic technology.

Applicants should submit a curriculum vitae, two-page summary of research accomplishments and future plans. Applicants should arrange to have 3-5 letters of recommendation sent to the search committee.

Please e-mail application materials to: [neurosciencesearch@utsouthwestern.edu](mailto:neurosciencesearch@utsouthwestern.edu), Neuroscience Search Committee, The University of Texas Southwestern Medical Center at Dallas, 5323 Harry Hines Blvd., Dallas, TX 75390-9111. The deadline for receipt of applications is November 1, 2012.

*The University of Texas Southwestern Medical Center is an Affirmative Action/Equal Opportunity Employer. Women and minority candidates are encouraged to apply.*



The Department of Biochemistry at Purdue University, West Lafayette, Indiana invites applications for a tenure track faculty position at the Assistant or Associate Professor level. The search will be focused on identifying researchers addressing critical questions in mechanistic protein biochemistry including, but not limited to, protein structure/function relationships and metabolic pathway analysis in plants, microorganisms, or animals. Applicants whose research is enabled by interdisciplinary approaches such as genomics and bioinformatics, single molecule analyses, synthetic biology or chemical biology will be of particular interest. The successful candidate will be expected to develop an internationally-recognized research program, interact with diverse faculty, staff and students across campus, demonstrate excellence in teaching and function as an active member of the department and university faculty.

The Department of Biochemistry is a small, interactive, and collegial community of researchers that contributes significantly to the vibrant life science community of Purdue University. Our faculty participate in interdisciplinary programs in plant biology, genetics, bioinformatics, cancer, neuroscience, and biophysics. Support facilities are available for genomic analysis, metabolomics, protein mass spectrometry, NMR, X-ray crystallography, microscopy, and transgenic animal research. For more information see [www.biochem.purdue.edu](http://www.biochem.purdue.edu).

Applicants for assistant professor should have a Ph.D. or equivalent degree in biochemistry, biophysics, computational biology or a related field and at least two years of post-doctoral experience. Successful candidates should have a strong publication record, the potential to develop a vigorous, extramurally-funded research program, and a commitment to research and teaching excellence. Candidates at the associate professor level must have a track record of academic achievement and external funding in addition to the above. Applications should include a cover letter, curriculum vitae, two-page summary of research interests, one-page teaching statement and the names and contact information of three references. Applications should be submitted electronically to [biochem-search@purdue.edu](mailto:biochem-search@purdue.edu). Screening of applications will begin **October 8, 2012** and will continue until the position is filled. A background check will be required for employment in this position.

*Purdue University is an Equal Opportunity/Equal Access/Affirmative Action Employer fully committed to achieving a diverse workforce.*



## Environmental Plant Physiologist Assistant Professor School of Biological Sciences College of Arts and Sciences

The School of Biological Sciences at Washington State University, Pullman, Washington, invites applications for a full-time, permanent, tenure-track faculty position in environmental plant physiology. This position is to be filled at the Assistant Professor level and will begin in August of 2013. Candidates should have integrative research that addresses the physiological adaptation of plants at the organ/whole plant level to changing environmental conditions. Candidates will be expected to apply modern physiological methods, coupled with developing techniques, in research on the mechanisms (e.g., signaling processes, gene and biochemical regulation) controlling the plasticity of plants to optimize physiological processes, such as photosynthesis, primary metabolism, and growth.

Required qualifications include an earned doctorate at time of application, a record of research accomplishment in environmental plant physiology, record of ability to teach undergraduate and graduate courses in plant biology, including physiology, effective communication skills, and demonstrated ability to collaborate with other scientists. Successful candidates will be expected to develop and maintain an active research program supported by extramural funding, train graduate and undergraduate students, participate in graduate and undergraduate teaching, participate in service needs, and advance our commitment to diversity and multiculturalism.

To apply, visit [www.wsujobs.com](http://www.wsujobs.com) to upload application materials. Applications must include a letter of application addressing qualifications, a curriculum vitae, separate teaching and research statements and up to three (3) selected reprints of published or in press papers. Three (3) letters of recommendation that address the applicant's history of and potential for research, teaching and communication excellence are required. The reference letters will be automatically requested and obtained from the reference provider through our online application system. Review of applications begins **November 1, 2012**. For information on the position or the status of your application, candidates may contact **Dr. Michael Knoblauch** ([knoblauch@wsu.edu](mailto:knoblauch@wsu.edu)). Full notice of vacancy can be viewed at <https://www.wsujobs.com>.

EEO/AA/AD

## THE UNIVERSITY of TENNESSEE KNOXVILLE COLLEGE OF ARTS & SCIENCES

### Physical Biochemist/Biophysicist

The Biochemistry and Cellular and Molecular Biology Department (BCMB) at the University of Tennessee at Knoxville (UTK) is soliciting applications for a full-time, tenure-track position at the rank of ASSISTANT PROFESSOR, to begin August 1, 2013. The BCMB Department (<http://web.bio.utk.edu/bcmb>) has 32 faculty members with core strengths in structural biology, plant biology, and developmental genetics. We seek applicants who use contemporary experimental biophysical methods to explore fundamental molecular, cellular, or physiological processes. The ideal candidate will develop an innovative and extramurally funded research program that complements existing areas of strength including membrane structure/function, protein trafficking, signal transduction, chromatin structure, and enzyme structure/function.

Applicants must have a Ph.D. and postdoctoral experience in an appropriate discipline with evidence of high quality research, a strong commitment to teaching, and the ability to teach introductory biochemistry and/or physical biochemistry as well as more advanced graduate courses in their area. Applicants should send a single PDF containing a cover letter, *curriculum vitae*, concise outline of current and future research interests, and statement of teaching effectiveness to [biophysical@utk.edu](mailto:biophysical@utk.edu). Applicants should arrange for three letters of recommendation to be sent electronically to [referenceletters@utk.edu](mailto:referenceletters@utk.edu). Further inquiries can be directed to **Dr. Barry D. Bruce**, (865-974-4082; [bbruce@utk.edu](mailto:bbruce@utk.edu)). Review of applications will begin on **October 15, 2012** continue until the position is filled.

The Knoxville campus of the University of Tennessee is seeking candidates who have the ability to contribute in meaningful ways to the diversity and intercultural goals of the University.

*The University of Tennessee is an EEO/AA/Title VI/Title IX/Section 504/ADA/ADEA institution in the provision of its education and employment programs and services. All qualified applicants will receive equal consideration for employment without regard to race, color, national origin, religion, sex, pregnancy, marital status, sexual orientation, gender identity, age, physical or mental disability, or covered veteran status.*



### Tenure Track Assistant Professor Developmental Biologist

The Department of Developmental Biology at Washington University School of Medicine is undergoing a major expansion and invites applications at the level of assistant professor on the tenure track. We are seeking outstanding colleagues with an interest in any area of developmental biology, including the genetic and epigenetic mechanisms of mammalian embryogenesis, cell fate specification and reprogramming, tissue engineering, and the roles of membrane channels and receptors in development and differentiation. Faculty in the Department of Developmental Biology employ a broad range of cell culture systems and model organisms, including *C. elegans*, *D. melanogaster*, *Xenopus*, zebrafish and mouse. (Please visit our website at <http://devbio.wustl.edu/index.htm>)

Review of applications will start **October 15, 2012**. Interested applicants should email a single PDF file of their curriculum vitae, summary of their research accomplishments and plans, and should also arrange to have three letters of recommendation emailed to:

**Search Committee (c/o Lilianna Solnica-Krezel, Ph.D.)**  
Department of Developmental Biology  
Washington University School of Medicine  
660 South Euclid Avenue  
Campus Box 8103  
St. Louis, MO 63110  
Email: [devbiosearch@wustl.edu](mailto:devbiosearch@wustl.edu)

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Equal Opportunity Employer AA/EOE M/F/D/V.*



### NEUROPHYSIOLOGIST Tenure-Track Faculty Position Biology Department Williams College

The Biology Department at Williams College, a premier liberal arts college with a long-standing tradition of excellence in the sciences, invites applications for a tenure-track position at the rank of Assistant Professor, to begin July 2013. We seek a broadly-trained scientist who studies neurons at the cellular level and incorporates techniques such as optogenetics or electrophysiology in their research program. The candidate is expected to develop a research program that attracts extramural funding and involves undergraduates. Start-up funds and internal funding for research are available. Normally, faculty members teach one course and two laboratory sections (or the equivalent) each semester. The candidate is expected to teach an animal physiology course, upper-level courses in the applicant's specialty and introductory courses within the biology department and Neuroscience Program.

A Ph.D., postdoctoral experience, and a strong research record are required. We anticipate an appointment at the beginning assistant professor level, although a more senior appointment is possible under special circumstances. All offers of employment are contingent upon completion of a background check. Applicants should submit curriculum vitae, brief statements of teaching and research interests, and arrange for three letters of recommendation to be sent by **November 2, 2012**, to: [neurosearch@williams.edu](mailto:neurosearch@williams.edu), care of **Steven Swoap, Chair, Department of Biology, Williams College**.

Williams College is a coeducational liberal arts institution located in the Berkshire Hills of western Massachusetts with easy access to the culturally rich cities of Albany, Boston, and New York City. The College is committed to building and supporting a diverse population of approximately 2,000 students, and to fostering an inclusive faculty, staff and curriculum. Williams has built its reputation on outstanding teaching and scholarship and on the academic excellence of its students. Please visit the Williams College website (<http://www.williams.edu>).

*Beyond meeting fully its legal obligations for non-discrimination, Williams College is committed to building a diverse and inclusive community where members from all backgrounds can live, learn, and thrive.*



### The University of Texas at Austin Assistant/Associate Professor in Cell Biology

The Section of Molecular Cell and Developmental Biology invites applications for a tenure-track or tenured Assistant/Associate Professor position. We seek an outstanding junior or mid-career investigator who will build an active research program in eukaryotic cell biology and who will teach effectively at the undergraduate and graduate levels. We are particularly interested in applicants who bridge or build on existing research strengths within the Section to address important questions in any area of cell biology. The successful applicant will be joining the biology community at UT-Austin during an exciting phase of growth, with recent hires in cell biology, developmental biology, plant biology, neuroscience, cancer biology, and related areas. Very generous start-up funds are available, and the successful candidate will also be eligible for affiliation with the Institute for Cellular and Molecular Biology, which provides state-of-the-art facilities and supports an excellent graduate program.

Austin is located in the Texas hill country and is widely recognized as one of America's most beautiful and liveable cities.

Please send a single PDF file containing a cover letter, CV, 2-3 page statement of current and future research directions and a 1 page teaching statement to: [MCDB\\_cell\\_bio@austin.utexas.edu](mailto:MCDB_cell_bio@austin.utexas.edu)

Please have 3 letters of reference sent as PDF files to the e-mail address above. Completed applications received by **November 1, 2012** will receive first consideration, and applications will continue to be accepted until the position is filled.

home pages: <http://www.biosci.utexas.edu/MCDB/> and <http://www.icmb.utexas.edu/>

*The University of Texas, Austin is an Equal Opportunity Employer that values diversity in its work force. Women and minorities are encouraged to apply. A background check will be conducted on applicant selected.*



### The University of Texas at Austin Plant Molecular Biology Position

The Section of Molecular Cell and Developmental Biology invites applications for a tenure-track Assistant Professor position. We seek an outstanding investigator who will build an active research program and who will teach effectively at undergraduate and graduate levels. We seek applications from individuals who use contemporary approaches to address fundamental questions in any area of plant biology, including but not limited to epigenetics, genetics, genomics, RNA biology, cell biology, and developmental biology. The successful applicant will be joining the biology community at UT-Austin during an exciting phase of growth, with recent hires in developmental biology, plant biology, systems biology, neurobiology, and related areas. Very generous start-up funds are available, and the successful candidate will be eligible for affiliation with the Institute for Cellular and Molecular Biology, which provides state-of-the-art facilities and supports an excellent graduate program. The successful candidate will also be affiliated with the plant biology graduate program.

Austin is located in the Texas hill country and is widely recognized as one of America's most beautiful and liveable cities.

Please send a single PDF file containing a cover letter, CV, 2-4 page statement of current and future research directions and a 1 page teaching statement to: [MCDB\\_plantbio@austin.utexas.edu](mailto:MCDB_plantbio@austin.utexas.edu)

Please also request 3 letters of reference to be sent as PDF files directly to the e-mail address above. Completed applications received by **November 1, 2012** will receive first consideration, but applications will continue to be accepted until the position is filled.

home pages: <http://www.biosci.utexas.edu/MCDB/>; <http://www.icmb.utexas.edu/> and <http://www.biosci.utexas.edu/graduate/plantbio/>

*The University of Texas, Austin is an Equal Opportunity Employer that values diversity in its work force. Women and minorities are encouraged to apply. A background check will be conducted on the applicant selected.*



Stanford University Medical Center

### Basic or Translational Vision Science Faculty Position

The Stanford Institute for Neuro-Innovation and Translational Neurosciences (SINTN) and the Department of Ophthalmology seek to appoint a new faculty member in the area of basic or translational vision science. In addition to leading a research laboratory, the faculty member will be expected to mentor students and post-doctoral fellows. The appointment will be made at the Assistant, Associate or Full Professor level in the University Tenure Line, commensurate with the applicant's experience. The predominant criterion for appointment in the University Tenure Line is a major commitment to research and teaching.

Please submit a curriculum vitae, statement of research interests and 3 reference letters via [academicjobsonline.org](http://academicjobsonline.org) by October 31, 2012 to:

**Brian Wandell, PhD**  
Isaac and Madeline Stein Family Chair  
Director, Stanford's Center for Neurobiological Imaging  
Chair, Search Committee  
c/o Kristy Verhines  
Stanford University School of Medicine  
Lorry Lokey Stem Cell Research Building, G1078  
265 Campus Drive  
Stanford, CA 94305-5453

*Stanford University is an Equal Opportunity Employer and is committed to increasing the diversity of its faculty. It welcomes nominations of and applications from women and members of minority groups, as well as others who would bring additional dimensions to the university's research and teaching missions.*



UNIVERSITY of  
**ROCHESTER**  
MEDICAL CENTER

### James P. Wilmot Cancer Center Faculty Position

The James P. Wilmot Cancer Center at the University of Rochester Medical Center will recruit a tenure-track faculty member at any level with expertise in the area of head and neck cancer research. The successful candidate will be a member of the newly established head and neck cancer program, be affiliated with a fitting academic department and benefit from a multidisciplinary and highly interactive research community, a vibrant graduate program and state of the art infrastructure and core facilities at the University of Rochester.

Qualified candidates who study basic science and/or translational aspects of head and neck cancer are invited to apply to the search committee. Candidates with a strong record of accomplishment should submit a CV, statement of research interests/plans, pdfs of two publications, and arrange to have three letters of recommendation sent to: [tina\\_faugh@urmc.rochester.edu](mailto:tina_faugh@urmc.rochester.edu).

Review of applications will start **October 15<sup>th</sup>, 2012**.

*The University of Rochester is an Equal Opportunity Employer and has a strong commitment to diversity and actively encourages applications from candidates from groups underrepresented in higher education.*



Albert Einstein College of Medicine  
OF YESHIVA UNIVERSITY

Chair

### Dominick P. Purpura Department of Neuroscience

The Albert Einstein College of Medicine invites applications and nominations for the position of Chair of the Dominick P. Purpura Department of Neuroscience. We seek an outstanding scientist with leadership experience and a broad vision for Neuroscience, for appointment as Professor and holder of an endowed chair.

Einstein offers a supportive research environment with numerous, well-equipped core facilities (<http://www.einstein.yu.edu/home>). Einstein is one of the nation's premier research-intensive medical schools, with a full-time faculty of 2,585 physicians and scientists, 759 MD students, 339 PhD students, 117 MD/PhD students, and 395 Postdoctoral fellows. Einstein has NIH funded research centers in Human Embryonic Stem Cells, Aging, AIDS, Cancer, Diabetes, Obesity, Health Disparities, Intellectual and Developmental Disabilities and Liver Diseases.

The Department of Neuroscience <http://www.einstein.yu.edu/departments/neuroscience/> at Einstein offers an interactive, translational and diverse environment, including outstanding and well-funded scientists in the fields of cognitive, behavioral, physiological and cellular and molecular neuroscience. The Department of Neuroscience consists of 27 Primary Faculty, 30 Secondary Faculty, 26 post docs, 32 graduate students and 7 MSTP students. It is housed entirely within the 9 floors of the Rose F. Kennedy Research Building and has close interactions with the departments of Neurology and Psychiatry. It has 12,000 square feet of available laboratory space for new faculty recruitments. The College has made the recruitment of the Chair a primary goal and has committed substantial resources for recruitment and research support.

Please submit a letter and curriculum vitae in electronic format to **Dr. Robert H. Singer, Chair, Dominick P. Purpura Department of Neuroscience Search Committee, Albert Einstein College of Medicine, Jack and Pearl Resnick Campus, 1300 Morris Park Avenue, 601-Golding, Bronx, NY 10461. E-mail: [Robert.singer@einstein.yu.edu](mailto:Robert.singer@einstein.yu.edu)**.

*We particularly welcome applicants who will add diversity to our academic leadership and faculty. Equal Opportunity Employer.*



COLUMBIA UNIVERSITY  
IN THE CITY OF NEW YORK

### Neuroscience Faculty Recruitment

The Department of Neuroscience at Columbia University is currently recruiting faculty in the neurosciences, with a primary emphasis on three research areas: (1) cognitive and/or motor processes in awake, nonhuman primates; (2) linking neural circuitry and behavior in genetically tractable mammalian systems; and (3) molecular, cellular, and/or developmental neuroscience. In a cover letter, please direct your application to one of these three research areas. In exceptional circumstances, we will also consider applications in areas more distantly related to these three primary research themes. We encourage applications at all levels of seniority, from assistant to full professor.

Columbia University has an exceptionally strong and broad program in the neurosciences and aims to enhance interactions between basic and clinical research and to link the neurosciences with a wide range of other disciplines within the University. New faculty will be affiliated with the Department of Neuroscience, with the Doctoral Program in Neurobiology and Behavior, and with a newly established Mind Brain Behavior Institute. In addition, there are numerous opportunities for interaction with other scientific departments and programs at the Medical Center and Morningside Heights campuses.

The application deadline is November 30, 2012. Please submit applications online at <https://academicjobs.columbia.edu/applicants/Central?quickFind=56746> and include a cover letter, curriculum vitae, and a statement of research interests. In addition, please arrange for three references to submit letters of recommendation.

*Columbia University takes affirmative action to ensure equal opportunity.*





# NORTHWESTERN UNIVERSITY

## ASSISTANT PROFESSOR

The Department of Molecular BioSciences encourages outstanding individuals with research interests that complement existing strengths of the department to apply for tenure-track appointments at the level of **Assistant Professor**. The department is an exciting interdisciplinary research and training environment located on Northwestern's Evanston, Illinois campus (<http://www.molbiosci.northwestern.edu>). Current faculty research interests encompass biochemistry, cell and developmental biology, structural biology and molecular biology.

### We are particularly interested in the following areas:

- Biophysical approaches to study protein-protein or protein-nucleic acid interactions.
- Systems Biology, especially those using high-throughput approaches to study biological complexity, synthetic biology, or developmental networks.

Applicants should prepare a cover letter, curriculum vitae, statement of teaching experience and interests, research summary, and a statement of future research goals. For further instructions and to submit the application, please visit the Molecular BioSciences homepage at <http://www.molbiosci.northwestern.edu>. Applicants should arrange for at least three letters of recommendation to be submitted on their behalf. Questions should be sent to [molbiosciseach@northwestern.edu](mailto:molbiosciseach@northwestern.edu). To ensure full consideration, please submit all materials by **November 1, 2012**.

*Northwestern University is an Affirmative Action/Equal Opportunity Employer. Women and underrepresented minorities are especially encouraged to apply.*



## Duke University Medical Center

The Department of Radiation Oncology at Duke University Medical Center (DUMC) is seeking a physician scientist, veterinary scientist, or scientist to join the Department of Radiation Oncology and the Radiation Oncology & Imaging Program in the Duke Cancer Institute (DCI). The successful applicant will join a critical mass of radiation biologists at Duke, which includes a Center for Medical Countermeasures Against Radiation and a NASA Specialized Center of Research. Depending on the applicant's background and interests, this tenure track position may have the opportunity for secondary appointments in other clinical departments and basic science departments and robust collaboration with established investigators plus the opportunity to train graduate students. An investigator with at least two years of post-doctoral research experience and a successful track record of publications is required. A previous history of peer reviewed external funding is desirable. The successful candidate will have the opportunity to collaborate with clinical colleagues and facilitate the design and implementation of innovative early phase clinical trials. It is anticipated that the successful candidate will be able to span basic and translational research to promote further development of translational research programs in the department and the DCI. This faculty member will also assist in teaching medical students, residents, and fellows. Depending on clinical expertise and research interest, clinically trained applicants will have the opportunity to subspecialize in the care of cancer patients. Applicants will be considered at the Assistant or Associate Professor level.

Faculty members within DUMC have access to many core facilities including tissue bio-banking, animal facilities with state of the art imaging and small-animal irradiation, advanced clinical imaging, biostatistics, and other outstanding resources. Duke University Medical Center is located in Durham, North Carolina. Duke University Hospital and the School of Medicine are ranked among the top institutions in the United States. Duke University is an Affirmative Action and Equal Opportunity Employer. Women and minorities are encouraged to apply.

**Requirements:** Applicants must have MD, MD/PhD, DVM, DVM/PhD or PhD degrees, demonstrated excellence in laboratory research and experience or interest in translational research and/or clinical trial design. Please send a letter of inquiry, curriculum vitae, reference list, and description of prior experience and future plans to: **Christopher Willett, MD, Chairman of Radiation Oncology, c/o Donna Wimberley** ([donna.wimberley@duke.edu](mailto:donna.wimberley@duke.edu)), DUMC Box 3085, Durham, NC 27710.



*FGCU invites highly qualified applicants to apply to the following positions:*

### College of Arts & Sciences

**Chemistry, Instructor I, Req. # 1646**  
**Chemistry, Assistant Professor, Req. #1650**

**Plant Systematics, Assistant/Associate/ Full Professor, Req. #1656**

To apply, please visit our website at <http://jobs.fgcu.edu> and access the Req. # for detailed information and deadline dates. **Application materials will only be accepted online.** All application materials must be received by the deadline date of the position. **Application packages, including additional materials submitted such as videos, tapes, slides, books, etc., are subject to public review under Florida's Public Records law, shall become the property of FGCU, and cannot be returned.** Finalists will be required to provide official transcripts.

*Equal Opportunity/Equal Access Employer. FGCU has a commitment to cultural, racial, and ethnic communities and encourages women and minorities to apply.*

## UT SOUTHWESTERN MEDICAL CENTER

### Assistant Professor of Biochemistry

The Department of Biochemistry at The University of Texas Southwestern Medical Center invites applications from candidates for a tenure-track faculty position at the rank of Assistant Professor. Candidates should be engaged in innovative research within the broad fields of biochemistry or molecular biology. UT Southwestern maintains state-of-the-art facilities and employs a faculty that includes five Nobel Laureates and nineteen members of the National Academy of Sciences. The Biochemistry Department offers a vibrant environment for research, generous start-up support, and participation in graduate-level teaching.

Applicants should submit a **curriculum vitae**, a concise description of research plans, and three letters of reference by **December 1, 2012** to the attention of Dr. Steven L. McKnight, Chair, Department of Biochemistry at [Biochem.Search@UTSouthwestern.edu](mailto:Biochem.Search@UTSouthwestern.edu).

*The University of Texas Southwestern Medical Center is an Affirmative Action/ Equal Opportunity Employer. Women and minority candidates are encouraged to apply.*



University of California  
San Francisco

The Department of Urology at the University of California, San Francisco, is recruiting for a full-time faculty basic research scientist at the Associate/Full Adjunct Professor level. Applicants should have a Ph.D. or equivalent degree in one of the following areas: molecular biology, genetics, virology, microbiology, biochemistry or biology. Candidates should have solid research experience supported by a track record of publications. Prior research experience in stress incontinence and erectile dysfunction diseases is preferred and a commitment in education. Please submit curriculum vitae, a brief statement of your research interest, and three letters of reference to:

**Peter R. Carroll, MD**  
**Professor and Chair, UCSF Department of Urology**  
**Attention: Penny Chee**  
**400 Parnassus, A628**  
**San Francisco, CA 94143-0738**

*UCSF seeks candidates whose experience, teaching, research, or community service has prepared them to contribute to our commitment of diversity and excellence. The University is an Equal Opportunity/ Affirmative Action Employer. All qualified applicants are encouraged to apply, including minorities and women.*



## Georgia Health Sciences University

### Associate Professor – Professor Center for Biotechnology and Genomic Medicine

We seek distinguished investigators to join the Center for Biotechnology & Genomic Medicine (CBGM) at Georgia Health Sciences University. We currently have two faculty positions open at the Associate Professor to Professor Level. These positions will be part of a well-funded and growing team of researchers that are dedicated to advancing translational research through the use of modern high throughput technologies. The positions require a doctoral degree and additional research experience and extramural funding. The CBGM is currently looking for applicants with expertise in the following disciplines: Glycomics, Epigenetics/Epigenomics, Metabolomics and Drug Discovery.

Send CV, 3 references, and research plans to the center director: **Jin-Xiong She, Ph.D., Center for Biotechnology and Genomic Medicine, GHSU, 1120 15<sup>th</sup> Street, CA-4124, Augusta, GA 30912-2400. Email: jshe@georgiahealth.edu.**

All applicants must apply through [www.georgiahealth.edu/facultyjobs](http://www.georgiahealth.edu/facultyjobs).

**The Georgia Health Sciences University (GHSU)** is the health sciences campus of the University System of Georgia. It is located in a historic city of Augusta, Georgia with excellent recreational and lifestyle opportunities. Searches are part of a 5-year initiative to recruit 10 new research scientists to the CBGM at GHSU. Review of applications will begin **October 1, 2012**, and will continue until the positions are filled.

*Applications from women and members of under-represented minority groups encouraged. EEO/AA/Equal Access Employer.*



### FACULTY POSITIONS IN BIOCHEMISTRY, MOLECULAR BIOLOGY, AND GENETICS

The Department of Biochemistry and Molecular Biology at the Penn State University College of Medicine is expanding under the new leadership of Dr. James R. Broach. The Department invites applications from outstanding scientists with Ph.D., M.D., or equivalent degrees for two full-time tenure-track positions. We seek candidates at the Assistant Professor level who have an active highly competitive independent research program or who show a strong potential to develop such a program. For one position (BMB1) we look for candidates in the areas of molecular biology, genetics, epigenetics, and/or genomics. For the other position (BMB2) we seek candidates who are using state-of-the-art Mass spectrometry-based methods to study protein expression (proteomics), metabolism (metabolomics), or the role of protein modification in its normal function and disease. For additional information, please visit the following website: <http://www2.med.psu.edu/biochemistry/>. Applicants should submit a curriculum vitae and a brief statement of research plans, and arrange for three letters of reference to be sent to Faculty Search Committee, **biochem\_apply@hmc.psu.edu** or to **Department of Biochemistry and Molecular Biology H171, Penn State University College of Medicine, Hershey PA 17033**. Application should be received prior to **November 15, 2012**.

*Employment will require successful completion of background check(s) in accordance with University policies. Penn State is committed to Affirmative Action, Equal Opportunity and the diversity of its workforce.*



### The University of Oklahoma Assistant Professor Structural Biology

The Department of Chemistry and Biochemistry at the University of Oklahoma invites applications for a tenure-track faculty position at the rank of Assistant Professor beginning August 16, 2013. We are especially interested in applicants with biochemistry expertise who use macromolecular X-ray crystallography to investigate drug interactions with biologically relevant targets. The successful candidate will become an active member in the Oklahoma Center of Biomedical Research Excellence (CoBRE) in Structural Biology (OCSB) and the Institute for Natural Products Applications and Research Technologies (INPART). Both units are located in the Stephenson Life Sciences Research Center on the University of Oklahoma Research Campus (<http://urc.ou.edu>). The successful candidate is expected to establish a productive and externally funded research program that involves collaborations among OCSB and INPART members, as well as contribute to the department's graduate and undergraduate teaching missions; normal teaching expectation is one major course per semester. Applicants must have completed a Ph.D. degree in chemistry, biochemistry, or a closely related field (postdoctoral experience preferred) by the appointment start date.

Interested individuals should submit a single PDF file to **biochemsrch@ou.edu** containing the following: a cover letter describing their interest in this position, a curriculum vita, a description of research accomplishments and future research plans (6 page limit), and a statement of teaching experience and interests. Candidates should also request three letters of recommendation and have them sent directly to **biochemsrch@ou.edu**. To ensure full consideration, all application materials should be received by October 22, 2012. This position will remain open until filled. For more information, visit <http://chem.ou.edu>.

*The University of Oklahoma is an equal opportunity institution. [www.ou.edu/eoo](http://www.ou.edu/eoo)*



### The University of Oklahoma Assistant Professor Natural Products Drug Development

The Department of Chemistry and Biochemistry at the University of Oklahoma invites applications for a tenure-track faculty position at the rank of Assistant Professor beginning August 16, 2013. We are especially interested in applicants with chemistry and biochemistry expertise who investigate the drug development applications of natural products using medicinal chemistry, biosynthesis, and/or total synthesis approaches. The successful candidate will become an active member in the Institute for Natural Products Applications and Research Technologies (INPART), which is located in the Stephenson Life Sciences Research Center on the University of Oklahoma Research Campus (<http://urc.ou.edu>). The successful candidate is expected to establish a productive and externally funded research program that involves collaborations among INPART members, as well as contribute to the department's graduate and undergraduate teaching missions; normal teaching expectation is one major course per semester. Applicants must have completed a Ph.D. degree in natural products chemistry, biochemistry, or a closely related field (postdoctoral experience preferred) by the time of appointment.

Interested individuals should submit a single PDF file to **chemsrch@ou.edu** containing the following: a cover letter describing their interest in this position, a curriculum vita, a description of research accomplishments and future research plans (6 page limit), and a statement of teaching experience and interests. Candidates should also request three letters of recommendation and have them sent directly to **chemsrch@ou.edu**. To ensure full consideration, all application materials should be received by October 22, 2012. This position will remain open until filled. For more information, visit <http://chem.ou.edu>.

*The University of Oklahoma is an equal opportunity institution. [www.ou.edu/eoo](http://www.ou.edu/eoo)*

# There's only one

## DR. SHIRLEY MALCOM



To Dr. Shirley Malcom, born and raised in the segregated South more than 65 years ago, a career based on her studies in science seemed even less likely than the launch of the Soviet's Sputnik. But with Sputnik's success, the Space Race officially started and, in an instant, brought a laser-like focus to science education and ways to deliver a proper response. Not long after, Dr. Malcom entered the picture.

Although black schools at the time received fewer dollars per student and did not have sufficient resources to maintain their labs at a level equivalent to the white schools, Dr. Malcom found her way to the University of Washington where she succeeded in obtaining a B.S. in spite of the difficulties of being an African American woman in the field of science. From there she went on to earn a Ph.D. in ecology from Penn State and held a faculty position at the University of North Carolina, Wilmington.

Dr. Malcom has served at the AAAS in multiple capacities, and is presently Head of the Directorate for Education and Human Resources Programs. Nominated by President Clinton to the National Science Board, she also held a position on his Committee of Advisors on Science and Technology. She is currently a member of the Caltech Board of Trustees, a Regent of Morgan State University, and co-chair of the Gender Advisory Board of the UN Commission on Science and Technology for Development. She has held numerous other positions of distinction and is the principal author of *The Double Bind: The Price of Being a Minority Woman in Science*.

Of her active career in science, Dr. Malcom says, "I guess I have become a poster child for taking one's science background and using that in many other ways: we ask questions; we try to understand what we find; we consider what evidence we would need to confirm or refute hypotheses. And that happens in whatever setting one finds oneself."

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**A'' Aalto University**

## Professor position in sustainable energy solutions

(Matti Pursula Chair)

The professor is expected to play a strong role in the multidisciplinary research and teaching activities relevant for sustainable and efficient energy solutions, and lead the recently started university-wide research programme (AEF).

The position will be placed in one of the four schools of science and technology depending on the field of the successful candidate.

Application deadline is November 15, 2012. For further information and application details, please visit at [aalto.fi/en/openpositions](http://aalto.fi/en/openpositions). More information on AEF-programme is available at [energyefficiency.aalto.fi/en](http://energyefficiency.aalto.fi/en)

**Aalto University** is a new university with over a century of experience. Created from a high-profile merger between three leading universities in Finland – the Helsinki School of Economics, Helsinki University of Technology and the University of Art and Design Helsinki – Aalto University opens up new possibilities for strong multidisciplinary education and research. Aalto University has 20 000 students and a staff of 5 000 including 350 professors.

*aalto.fi*



[www.ox.ac.uk/jobs](http://www.ox.ac.uk/jobs)

### University Lectureship in Biochemistry, Structural Biology and Biophysics –

in association with a Tutorial Fellowship at Lincoln College

**Salary £42,883 - £57,581 per annum**  
**Department of Biochemistry**

Applications are invited for a University Lectureship in Biochemistry in the area of Structural Biology and Biophysics. This position would be held within the Department of Biochemistry, University of Oxford, leading to a permanent academic post upon the successful completion of a probationary period. A Tutorial Fellowship at Lincoln College is attached to this position.

The successful applicant will join a team of structural biologists and biophysicists which forms a key element of research within the new Biochemistry Building. The principal duty will be to establish and lead a world-class research programme in the area of experimental structural biology and/or biophysics of membrane proteins and related systems. The successful applicant will have, or show promise of, an international reputation for research and scholarship, and will contribute to and benefit from a full role in the academic life of the Biochemistry Department and of Lincoln College. He/she will be able to demonstrate the ability to teach high-achieving and challenging undergraduates and graduate students.

Please see the further particulars on the website at <http://www.admin.ox.ac.uk/fp> for more details about the post and for full instructions before making an application. For an informal discussion, please contact Professor Mark Sansom, David Phillips Professor of Molecular Biophysics and Head of Department, on: (01865) 613 212 or [head@bioch.ox.ac.uk](mailto:head@bioch.ox.ac.uk). Applications should be sent by email to [academicrecruitment@bioch.ox.ac.uk](mailto:academicrecruitment@bioch.ox.ac.uk) by 12 noon on Friday 12 October 2012.

Applications are particularly welcome from women and ethnic minorities, who are under-represented in academic posts in Oxford.

**Committed to equality and valuing diversity**



[www.ox.ac.uk/jobs](http://www.ox.ac.uk/jobs)

### University Lectureship in Biochemistry, Membrane Protein Crystallography –

in association with an Official Studentship at Christ Church

**Salary £42,883 - £57,581 per annum**  
**Department of Biochemistry**

Applications are invited for a University Lectureship in Biochemistry in the area of Membrane Protein Crystallography. This position would be held within the Department of Biochemistry, University of Oxford, leading to a permanent academic post upon the successful completion of a probationary period. An Official Studentship (i.e. a tutorial fellowship) at Christ Church is attached to this position.

The successful applicant will join a team of structural biologists and biophysicists which forms a key element of research within the new Biochemistry Building. The principal duty will be to establish and lead a world-class research programme in the area of structural biology as applied to membrane proteins. The successful applicant will have, or show promise of, an international reputation for research and scholarship, and will contribute to and benefit from a full role in the academic life of the Biochemistry Department and of Christ Church. He/she will be able to demonstrate the ability to teach high-achieving and challenging undergraduates and graduate students.

Please see the further particulars on the website at <http://www.admin.ox.ac.uk/fp> for more details about the post and for full instructions before making an application. For an informal discussion, please contact Professor Mark Sansom, David Phillips Professor of Molecular Biophysics and Head of Department, on: (01865) 613212 or [head@bioch.ox.ac.uk](mailto:head@bioch.ox.ac.uk). Applications should be sent by email to [academicrecruitment@bioch.ox.ac.uk](mailto:academicrecruitment@bioch.ox.ac.uk) by 12 noon on Friday 12 October 2012.

Applications are particularly welcome from women and ethnic minorities, who are under-represented in academic posts in Oxford.

**Committed to equality and valuing diversity**



## PROGRAM OFFICER UNDERSEA MEDICINE

(Physiology, Biology, Bio-Medical Engineering, or Psychology)

The Office of Naval Research is seeking a qualified individual to manage sponsored basic/applied research and advanced technology development programs and projects in the broad area of undersea medicine. The sponsored efforts are conducted principally at U.S. universities and industry or federal laboratories. This is a Civil Service position at the NP-IV level (\$105,211-\$155,500/yr) depending on individual qualifications.

The position requires significant expertise and experience in conducting, managing, and publishing (as a principal investigator) high-quality biomedical research in one or more areas related to undersea medicine such as diving physiology, decompression illnesses, hyperbaric oxygen toxicity, and/or other health-and performance- related areas associated with manned undersea operations.

For information on qualifications and how to apply, see the links to our Job Announcements at <http://www.onr.navy.mil/en/career-job-opportunity/job-listing.aspx>. Applications must be submitted by close of business or postmarked as of the closing date noted in the job announcement. Please contact Sandra L. Rendon at [Sandra.Rendon.ctr@navy.mil](mailto:Sandra.Rendon.ctr@navy.mil) for more information.

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## Department of Stem Cell and Regenerative Biology (HSCRB) Harvard University

### POSTDOCTORAL FELLOWSHIPS

The Department of Stem Cell and Regenerative Biology is actively seeking postdoctoral fellows in a wide variety of fields within stem cell and regenerative biology. Some appointments are funded through research grants awarded to Faculty members and are ordinarily for one year, sometimes renewable; other appointments are possible through individual postdoctoral fellowships.

For information on these research opportunities, application instructions, and the list of Faculty members with current openings, please visit the HSCRB website: <http://www.hscrb.harvard.edu>.

*Harvard University is an Equal Opportunity/Affirmative Action Employer.*

## Harry S. Truman Fellowship in National Security Science and Engineering



Sandia National Laboratories is one of the country's largest research facilities employing nearly 8,500 people at major facilities in Albuquerque, New Mexico and Livermore, California. Please visit our website at [www.sandia.gov](http://www.sandia.gov).

We are seeking applicants for the **President Harry S. Truman Fellowship in National Security Science and Engineering**. Candidates for this position are expected to solve a major scientific or engineering problem in their thesis work or have provided a new approach or insight to a major problem, as evidenced by a recognized impact in their field.

Sandia's research focus areas are: bioscience, computing and information science, engineering science, materials science, nanodevices and microsystems, radiation effects and high energy density science, and geoscience.

Candidates must meet the following requirements: U.S. citizenship, the ability to obtain and maintain a DOE "Q" clearance, and a Ph.D. (3.5 undergraduate and 3.7 graduate GPA preferred), awarded within the past three years at the time of application, or completed Ph.D. requirements by commencement of appointment. Candidates must be seeking their first national laboratory appointment (pre postdoc internships included).

The Truman Fellowship is a three-year appointment normally beginning on October 1. The salary is \$110,900 plus benefits and additional funding for the chosen proposal. The deadline to apply is November 1st of each year.

For complete application instructions, please visit: [http://www.sandia.gov/careers/students\\_postdocs/fellowships/truman\\_fellowship.html](http://www.sandia.gov/careers/students_postdocs/fellowships/truman_fellowship.html)

Please submit the complete package to: Yolanda Moreno, Sandia National Laboratories, P.O. Box 5800, MS0359, Albuquerque, NM 87185-0359, or email [ymoreno@sandia.gov](mailto:ymoreno@sandia.gov). Please reference Job ID: 640971. All materials must be received by November 1, 2012.

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## AAAS is here – helping scientists achieve career success.

Every month, over 400,000 students and scientists visit ScienceCareers.org in search of the information, advice, and opportunities they need to take the next step in their careers.

A complete career resource, free to the public, *Science* Careers offers a suite of tools and services developed specifically for scientists. With hundreds of career development articles, webinars and downloadable booklets filled with practical advice, a community forum providing answers to career questions, and thousands of job listings in academia, government, and industry, *Science* Careers has helped countless individuals prepare themselves for successful careers.

As a AAAS member, your dues help AAAS make this service freely available to the scientific community. If you're not a member, join us. Together we can make a difference.

To learn more, visit [aaas.org/plusyou/sciencecareers](https://aaas.org/plusyou/sciencecareers)







## **AAAS is here – bringing scientific expertise to policy making.**

Good science policy is the result of politicians understanding science and scientists understanding policy. Toward this end, AAAS manages the Science & Technology Policy Fellowships program, which embeds scientists and engineers in the federal government for up to two years. From Congress to the State Department, each class of Fellows contributes to the policy-making process while getting hands-on experience at the intersection of science and policy. As a AAAS member your dues support these efforts. If you're not yet a AAAS member, join us. Together we can make a difference.

To learn more, visit [aaas.org/plusyou/fellows](https://aaas.org/plusyou/fellows)







## **AAAS is here** – Science Funding, Climate Regulation, Human Rights.

Around the world, governments turn to AAAS as an objective, multidisciplinary scientific authority to educate public officials and judicial figures on today's most pressing issues. And this is just one of the ways that AAAS is committed to advancing science to support a healthy and prosperous world. Join us. Together we can make a difference.

To learn more, visit [aaas.org/plusyou/policy](https://aaas.org/plusyou/policy)







## AAAS is here – bringing educational infrastructure to the developing world.

AAAS is helping the Rwandan government rebuild its educational infrastructure as a way to help drive economic growth and development. By providing materials such as the Project 2061 *Atlas of Science Literacy*, lesson plans from Science NetLinks, and access to *Science* digital libraries, AAAS is helping the people of Rwanda work toward a future built around science and technology. As a AAAS member your dues support these efforts. If you're not yet a AAAS member, join us. Together we can make a difference.

To learn more, visit [aaas.org/plusyou/rwanda](https://aaas.org/plusyou/rwanda)







## AAAS is here – promoting universal science literacy.

In 1985, AAAS founded Project 2061 with the goal of helping all Americans become literate in science, mathematics, and technology. With its landmark publications *Science for All Americans* and *Benchmarks for Science Literacy*, Project 2061 set out recommendations for what all students should know and be able to do in science, mathematics, and technology by the time they graduate from high school. Today, many of the state standards in the United States have drawn their content from Project 2061.

Every day Project 2061 staff use their expertise as teachers, researchers, and scientists to evaluate textbooks and assessments, create conceptual strand maps for educators, produce groundbreaking research and innovative books, CD-ROMs, and professional development workshops for educators, all in the service of achieving our goal of universal science literacy.

As a AAAS member, your dues help support Project 2061 as it works to improve science education. If you are not yet a AAAS member, join us. Together we can make a difference.

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### FACULTY POSITIONS

#### FACULTY POSITION

The Department of Molecular & Cellular Physiology invites applications for a tenure-track position at the level of **ASSISTANT PROFESSOR**. Successful applicants will be expected to develop an independent, nationally funded research program. Research areas are open, but preference will be given to individuals with an interest and record of achievement in the cardiovascular sciences. Information about the departmental research focus is available at **website: <http://www.shreveportphysiology.com>**. A generous startup package and appropriate space will be offered. Applicants should have a Doctorate degree and relevant post-doctoral experience. Applications will be reviewed as they are received until the position is filled. Send curriculum vitae and names of three references to: **D. Neil Granger, Ph.D., Boyd Professor & Head, Department of Molecular & Cellular Physiology, LSU Health Sciences Center, 1501 Kings Highway, Shreveport, Louisiana, 71130-3932; Fax: 318-675-6005; E-mail: [dgrang@lsuhsc.edu](mailto:dgrang@lsuhsc.edu)**.

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#### POSTDOCTORAL AND RESEARCH ASSISTANT POSITIONS Bioinformatics and Genomics of Gene Regulation University of Texas Southwestern Medical Center at Dallas

Seeking individuals with a Ph.D. or Master's degree in bioinformatics, computational biology, or genomics to study gene regulation on a global scale in the laboratory of **Dr. W. Lee Kraus**. Candidates should be proficient in programming and analysis of genomic data sets, and have experience working with biological systems. The Kraus laboratory has a number of exciting ongoing projects related to the genomics of signal-regulated gene expression (visit our laboratory site and view us on PubMed). The University of Texas Southwestern Medical Center provides a dynamic, collaborative, integrative, and cutting-edge research and training environment.

Candidates should submit curriculum vitae or resume, brief statement of interests and accomplishments, and a list of three references electronically to **e-mail: [lee.kraus@utsouthwestern.edu](mailto:lee.kraus@utsouthwestern.edu)**. Successful applicants will receive competitive pay and benefits.

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**David S. Gross, Ph.D.**  
 Department of Biochemistry and  
 Molecular Biology  
 Louisiana State University  
 Health Sciences Center  
 Shreveport, LA USA  
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## Finding Balance: The Professor/Entrepreneur

### In This Issue

The science of biology is one thing but the science of business is another animal all together. For academics who recognize that their discovery or innovation can be commercialized into a product or service for which people will actually pay, the promise of entrepreneurial endeavors can be exhilarating and confounding at the same time. Issues of intellectual property ownership, human resources protocols, and time management, as well as the challenge of keeping a delineated barrier between professional and business activities can be difficult to manage, but these concerns shouldn't prevent academics from seeking to create a startup company. The key is to find avenues to balance the two worlds so that scientists can still continue to excel in what they do best and enjoy most—research and discovery.



See full story on page 1368.

### Upcoming Features

Top Employers Survey—September 21 (online); October 19 (print)

China Regional Focus—September 28

European Regional Focus—November 9

## SCIENCE & DIPLOMACY

Launched in March 2012, **SCIENCE & DIPLOMACY** provides an open access forum for rigorous thought, analysis, and insight to serve stakeholders who develop, implement, and teach all aspects of science and diplomacy. Learn more about the latest ideas in science diplomacy and receive regular updates by following @SciDip on Twitter and registering for free at [www.sciencediplomacy.org/user/register](http://www.sciencediplomacy.org/user/register).



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## How do you engage?

## AAAS Early Career Award for Public Engagement with Science

Nominations are open **now through October 15** for the **AAAS Early Career Award for Public Engagement with Science**.

With this award, AAAS recognizes early-career scientists and engineers who demonstrate excellence in their contribution to public engagement with science activities. The award recipient will receive a monetary prize of \$5,000, a commemorative plaque, and complimentary registration and reimbursement of travel expenses to the 2013 AAAS Annual Meeting in Boston.

For eligibility information and instructions on submitting nominations, visit [www.aaas.org/go/PESaward](http://www.aaas.org/go/PESaward).

**Deadline October 15**



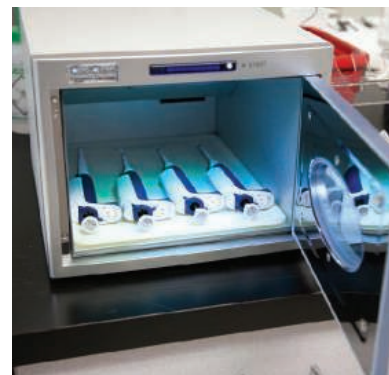
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